Tengsl líkamsþyngdarstuðuls og reykinga á meðgöngu við háþrýstingssjúkdóma barnshafandi kvenna

Lýðgrunduð tilfella-viðmiða rannsókn

Þuríður Anna Guðnadóttir

Ritgerð til meistaragráðu
Háskóli Íslands
Læknadeild
Námsbraut í lýðheilsuvísindum
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HÁSKÓLI ÍSLANDS

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Október 2014

Body Mass Index, Smoking and Hypertensive Disorders during pregnancy

Population based case control study

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Thesis for the degree of Master of Public Health Sciences

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October 2014

Prentun: Háskólaprent

Reykjavík, Ísland 2014

Ágrip

Markmið þessarar rannsóknar var að skoða tengsl reykinga og líkamsþyngdarstuðuls við háþrýstingssjúkdóma á meðgöngu, en til þeirra teljast langvinnur háþrýstingur, meðgönguháþrýstingur og meðgöngueitrun. Jafnframt var markmiðið að skoða samþætt áhrif líkamsþyngdarstuðuls og reykinga á þessa sjúkdóma.

Rannsóknin er tilfella-viðmiða rannsókn byggð á heildarhópi allra þungana á Íslandi 1989-2004, sem enduðu með fæðingum á Landspítala Háskólasjúkrahúsi. Fyrst voru valdar af handahófi 500 konur (tilfelli) með greindan háþrýstingssjúkdóm (samkvæmt ICD-10 flokkunarkerfinu, kóðar O10-16) á meðgöngu og án sykursýkisgreininga. Næst voru 1000 konur (viðmið) án háþrýstingsgreininga og án sykursýkisgreininga á meðgöngu valdar af handahófi úr Fæðingaskrá en þó paraðar við tilfelli eftir ártali fæðingar. Á móti einni sem hafði háþrýstingssjúkdóm voru því tvær sem höfðu ekki greindan háþrýstingssjúkdóm (1:2). Líkamsþyngdarstuðullinn (kg/m^2) var reiknaður út frá mælingum á hæð og þyngd í fyrstu mæðraskoðun. Til að leiðrétta fyrir áhrifum mögulegra blöndunar- og áhrifsþátta, og þannig meta sambandið, notuðum við lógístíska aðhvarfsgreiningu til að reikna út gagnlíkindahlutfall (OR), og 95% öryggisbil (CI). Tölfræðigreiningar voru gerðar þar sem Mantel-Haenzel aðferðin var notuð til að lagskipta eftir reykingum og fyrirburafæðingum.

Niðurstöðurnar sýndu að líkamsþyngdarstuðullinn snemma á meðgöngu hafði tengsl við allar tegundir háþrýstingssjúkdóma á meðgöngu (langvinnan háþrýsting, meðgönguháþrýsting og meðgöngueitrun). Borið saman við konur í kjörþyngd var leiðrétt gagnlíkindahlutfall (OR) fyrir allar tegundir háþrýstingssjúkdóma 1,8 (95% CI 1,3-2,3) hjá konum í yfirþyngd og 3,1 (CI 95% 2,2-4,3) hjá offeitum konum. OR fyrir allar tegundir háþrýstingssjúkdóma og offitu var hærra meðal kvenna sem reyktu (OR=3,9 95% CI 1,8-8,6) en þeirra sem reyktu ekki (OR=3,0 95% CI 2,1-4,3).

Niðurstöður þessar benda til þess að konur sem eru í ofþyngd og offitu séu í aukinni áhættu á að fá allar tegundir af háþrýstingssjúkdómum á meðgöngu borið saman við konur í kjörþyngd. Hættan eykst enn frekar ef þær reykja, þrátt fyrir að áður hafi verið sýnt fram á verndandi áhrif reykinga fyrir meðgöngueitrun og aðra háþrýstingssjúkdóma á meðgöngu.

Abstract

The purpose of this study was to investigate the association of smoking and body mass index with hypertensive disorders during pregnancy, including preexisting hypertension, gestational hypertension and preeclampsia. Further, to assess potentially combined effects of high body mass index and smoking on these disorders.

This is a case-control study based on national registers, nested within all pregnancies in Iceland 1989-2004, which resulted in birth at the Landspitali University Hospital. A total of 500 women were included as cases and 1000 as controls; matched on year of childbirth (1:2) and restricted to women with no registered diagnoses of pre-existing or gestational diabetes. Cases had a registered hypertensive disorder anytime during pregnancy (International Classification of Disease, 10th Revision, codes O10-16) and no registered diagnosis of gestational or pre-existing diabetes. Body mass index (kg/m^2) was based on early pregnancy height and weight measures. Adjusting for potential confounders, we used logistic regression models to calculate odds ratios (OR), and corresponding 95% confidence intervals (CI), as measures of association. Analyses were conducted stratified by smoking status and preterm births using the Mantel-Haenzel method.

The results showed that women's body mass index during early pregnancy was associated with all types of hypertensive disorders of pregnancy (preexisting hypertension, gestational hypertension and preeclampsia). Compared with normal weight women, the multivariable adjusted OR for any hypertensive disorder was 1.8 (95% CI 1.3-2.3) for overweight women and 3.1 (95% CI 2.2-4.3) for obese women. The OR for any hypertensive disorder with obesity was higher among smokers (OR=3.9, 95% CI 1.8-8.6) than non-smokers (OR=3.0, 95% CI 2.1-4.3).

The findings suggest that overweight and obese women are at considerable risk for all types of hypertensive disorders during pregnancy as compared with normal weight women. This risk is enhanced even further with smoking, despite the established inverse association of smoking with preeclampsia and other hypertensive disorders of pregnancy.

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Þakkir

Ég vil byrja á að þakka leiðbeinanda mínum, Helga Zoëga, fyrir frábært samstarf og ómetanlegan stuðning í öllu ferli þessarar rannsóknarvinnu. Fyrir að vera endalaust jákvæð og gefa sér tíma til að lesa yfir og koma með lærdómsríkar athugasemdir.

Unni Önnu Valdimarsdóttur og Ragnheiði I. Bjarnadóttur sem sátu í meistaranefndinni minni þakka ég fyrir góða leiðsögn og samstarf.

Sérstakar þakkir fá Drífa Pálín Geirs og Sigrún Helga Lund fyrir ómetanlega aðstoð við alla tölfræðivinnuna.

Starfsfólki Vesturhlíðar vil ég þakka fyrir að taka vel á móti mér og aðstoða mig í þá mánuði sem ég var hjá þeim að fletta í mæðraskrám.

Þá vil ég þakka Rannsóknarmiðstöð Íslands (RANNÍS) sem veitti fjárstyrk til rannsóknarinnar.

Fjölskyldu minni vil ég þakka fyrir að vera til staðar, styðja mig og hafa trú á mér og strákunum mínum Guðna Snæ, Ingva Frey og Óskari Mána, fyrir að sýna mömmu sinni þolinmæði og skilning.

Væntanlega hefði ég ekki sest á skólabekk að nýju nema fyrir hvatningu eiginmanns míns, Stefáns Brodda. Þolinmæði hans, stuðningur og aðstoð gerði mér kleift að vinna að þessu verkefni og sinna náminu síðustu ár.

Efnisyfirlit

Myndaskrá

Töfluskrá

Listi yfir skammstafanir

LÞS: Líkamsþyngdarstuðull

OR: Odds ratio, gagnlíkindahlutfall

CI: Confidence interval, öryggisbil

RR: Risk ratio, áhættuhlutfall

1 Inngangur

Lífsstíll fólks hefur mikil áhrif á heilsu þess og lífsstílsþættir hafa áhrif á dánartíðni og lífsgæði. Reykingar, hreyfingarleysi, óholl fæða, offita og aðrir lífsstílsþættir hafa verið tengdir við þróun ýmissa langvinnra sjúkdóma, svo sem krabbameins, hjartasjúkdóma, heilaæðasjúkdóma og sykursýki (1).

Hækkaður blóðþrýstingur er eitt af algengustu heilsufarsvandamálum vestrænna þjóða og hefur sterk tengsl við aðra hjartasjúkdóma. Talið er að um þriðjungur af fullorðnum Bandaríkjamönnum hafi háþrýsting (2). Greiningarskilmerkin fyrir hækkaðan blóðþrýsting eru þegar efri mörkin eru ≥ 140 mmHg og neðri mörkin ≥ 90 mmHg (3). Almennt hefur háþrýstingur ekki verið talinn vandamál kvenna á barneignaraldri (4). Bateman og félagar skoðuðu faraldsfræði háþrýstings meðal kvenna á barneignaraldri í Bandaríkjunum á árunum 1999-2008. Niðurstöður þeirra gáfu til kynna að um 8% kvenna á barneignaraldri (20-44 ára) hafi hækkaðan blóðþrýsting (5).

Mikið hefur áunnist í baráttunni við reykingar en samt sem áður eru þær enn stærsti orsakavaldur ótímabærra dauðadaga og veikinda í Evrópu. Reykingar hafa aukist á alþjóðavísu því þótt dregið hafi úr þeim á allra síðustu árum í þróaðari löndum hefur aukningin átt sér stað hjá fátækari þjóðum heims (6). Á síðustu árum hefur tíðni reykinga meðal evrópska karla verið á niðurleið en á sama tíma hefur orðið aukning í reykingum kvenna þá sérstaklega í mið-, austur- og suður-Evrópu (7). Samkvæmt nýjustu mælingum reykja um 11% Íslendinga daglega, 11% karla og 12% kvenna (8).

Algengi offitu í heiminum tvöfaldaðist á árunum 1980-2008 en talið er að 10% karla og 14% kvenna eldri en 20 ára séu haldin offitu (9). Á Íslandi hefur þróun offitu verið í sömu átt en hlutfall þeirra sem eru offeitir hækkaði mikið á síðustu tveimur áratugum. Hlutfall karla fór úr 7,2% í 18,9% meðan hlutfall kvenna fór úr 9,5% í 23,5% á árunum 1990-2007 (10). Ofþyngd og offita eru í dag fimmta algengasta dánarorsök í heiminum og tengjast fleiri dauðsföllum en undirþyngd (11). Offita er þekktur áhættuþáttur fyrir marga langvinna sjúkdóma svo sem sykursýki týpu 2, háþrýsting, kransæðasjúkdóma og heilaæðasjúkdóma (12).

Líkamsþyngdarstuðullinn (LÞS) er iðulega notaður til að skilgreina undirþyngd, kjörþyngd, ofþyngd og offitu. LÞS reiknast sem þyngd í hlutfalli við hæð (kg/m^2).

Flokkun fullorðinna út frá líkamsþyngdarstuðli

Flokkun	LÞS (kg/m²)
Undirþyngd	< 18,5
Kjörþyngd	18,5-24,9
Yfirþyngd	25,0-29,9
Offita	30,0-34,9
Mikil offita	> 35

Með tilliti til þess að lágmarka líkur á sjúkdómum er talið ákjósanlegast að vera í kjörþyngd en eftir því sem stuðullinn er hærri eru einstaklingar taldir útsettari fyrir sjúkdómum (9) .

Þó svo LÞS sé algengasta leiðin til að skilgreina þyngd þá er hann ekki án takmarkana. Hann tekur ekki tillit til fitudreifingar eða líkamssamsetningar þannig að þeir sem eru með mikla vöðvabyggingu geta mögulega verið rangt flokkaðir sem offeitir (13).

1.1 Háþrýstingssjúkdómar á meðgöngu

Fyrri rannsóknir hafa sýnt fram á að konur með hækkaðan blóðþrýsting eru mun líklegri en þær sem ekki hafa hækkaðan blóðþrýsting til að fá háþrýstingssjúkdóma á meðgöngu (14). Rannsókn á hópi unnin úr sjúkraskrám tvöhundruð og ellefu kvenna í Frakklandi sem greindar voru með langvinnan háþrýsting, og meðhöndlaðar með lyfjum, sýndi hins vegar að þær konur voru ekki í aukinni áhættu fyrir háþrýstingsjúkdóma á meðgöngu (15).

Þegar kemur að meðgöngu greinast 5-8% kvenna með háþrýstingssjúkdóma (3, 16). Mikil aukning hefur verið á greiningum á háþrýstingssjúkdómum á meðgöngu hjá bandarískum konum frá því um aldamótin. Að hluta til má líklega rekja ástæðuna til strangari greiningarskilmerkja (16). Háþrýstingur á meðgöngu er yfirleitt ekki langvinnt vandamál en hefur tengsl við auknar líkur á háþrýstingi og tengdum sjúkdómum í framtíðinni (17). Háþrýstingssjúkdómar eru þó ein af algengustu orsökum dauðsfalla kvenna á meðgöngu í vestrænum löndum (18). Í nýlegri rannsókn sem gerð var yfir þrettán ára tímabil í Hollandi þar sem skoðaðar voru ástæður dauðsfalla á meðgöngu, eða stuttu eftir fæðingu, sýnir að háþrýstingssjúkómar eru algengsta orsök dauðsfalla hjá mæðrum en í Hollandi hefur orðið aukning á dauðsföllum tengdum meðgöngu á síðustu árum (19). Alvarlegustu fylgikvillar þess að hafa hækkaðan blóðþrýsting á meðgöngu eru fylgjurof, blóðstorkusótt (disseminated intravascular coagulation), heilablæðingar, lifrarbilun og bráð nýrnabilun (3). Savitz og félagar skoðuðu tengsl háþrýstingssjúkóma á meðgöngu við langvinna sjúkdóma með því að tengja saman upplýsingar á fæðingarvottorðum við útskriftargreiningar frá sjúkrahúsum í New York ári eftir fæðingu, alls um 850,000 fæðingar. Þeirra niðurstöður sýndu að háþrýstingssjúkdómar á meðgöngu geti spáð fyrir um auknar líkur á innlögn á sjúkrahús vegna langvinnra sjúkdóma jafnvel innan árs frá fæðingu. Þau sáu tengsl við innlagnir vegna heilablóðfalla stuttu eftir fæðingu og tengsl við hjarta- og æðasjúkdóma, sem og efnaskiptavillu (metabolic syndrome) þegar lengra var liðið frá fæðingu. Þau benda á að mögulega séu einhverjir sameiginlegir þættir sem valda háþrýstingssjúkdómum á meðgöngu og langvinnum sjúkdómum eða þá að háþrýstingsjúkdómarnir hafi langvarandi áhrif á heilsu konunnar (20). Romundstad og félagar áÍykta um niðurstöður rannsóknar sem þau byggðu á gögnum úr norsku Fæðingaskránni að líklega megi rekja þessa tengingu til sameiginlegra áhættuþætta (21). Háþrýstingssjúkdómar hafa ekki eingöngu áhrif á móðurina því að ástandið skapar óhagstæðar aðstæður fyrir barnið í móðurkviði. Norsk lýðgrunduð rannsókn sem gerð var á öllum fæðingum í Noregi 1967-2006 sýndi að konur með hækkaðan blóðþrýsting eru mun líklegri til fæða andvana barn (eftir 20. viku meðgöngu) en konur með blóðþrýsting innan eðlilegra marka. Líkurnar eru þó mismunandi eftir því hvers kyns háþrýstingssjúkdómurinn er, en andvana fæðingum í Noregi hefur fækkað mikið á síðustu árum (22). Aðrar rannsóknir hafa gefið til kynna svipaðar niðurstöður (23). Háþrýstingssjúkdómar á meðgöngu hafa jafnframt í för með sér auknar líkur á fyrirburafæðingu og fæðingu léttbura (23-25).

Flokkun háþrýstingssjúkdóma á meðgöngu samkvæmt National High Blood Pressure Education Program (3)	
Háþrýstingssjúkdómur	**Skilgreining og einkenni**
Langvinnur háþrýstingur	Háþrýstingur* sem er til staðar fyrir meðgöngu eða er greindur fyrir 20. viku meðgöngu. Háþrýstingur sem greinist á meðgöngu og er enn til að staðar eftir fæðingu flokkast jafnframt sem langvinnur háþrýstingur.
Meðgöngueitrun	Meðgöngueitrun greinist hjá 3–5% kvenna á meðgöngu, þetta er fjölkerfasjúkdómur sem einkennist af hækkuðum blóðþrýstingi og prótínmagni sem er ≥300 mg í sólarhringsþvagi eða ≥1+ í strilmaprófi. Burðarmálskrampi, krampi hjá konum með meðgöngueitrun sem ekki er hægt að rekja til annarra orsaka err sjaldgæfur, en greinist í 0,1% meðgangna.
Meðgöngueitrun ofan á langvinnan háþrýsting	Allt að 30% kvenna með langvinnan háþrýsting greinast með meðgöngueitrun, þar sem prótínmiga bætist við á síðasta þriðjungi meðgöngunnar.
Meðgönguháþrýstingur	Í þennan flokk fara konur með meðgöngueitrun þar sem próteinmiga er ekki til staðar og konur sem eingöngu hafa hækkaðan blóðþrýsting sem greinist á seinni hluta meðgöngu. Ef blóðþrýstingur hefur ekki náð fyrri gildum 12 vikum eftir fæðingu barns er konan greind með langvinnan háþrýsting.

*Skilgreiningin á háþrýstingi er ef efri mörkin eru ≥140 mmHg eða neðri mörkin eru ≥90 mmHg í tveimur mælingum með a.m.k 4 klst á milli.

Orsakir þess að kona fær hækkaðan blóðþrýsting á meðgöngu eru mismunandi eftir því hvers kyns háþrýstingurinn er. Langvinnur háþrýstingur er ástand sem er til staðar fyrir meðgöngu eða greinist snemma á meðgöngunni (fyrir 20. viku meðgöngu). Í flestum tilfellum eru þessar konur með háþrýsting án undirliggjandi sjúkdóma (primary hypertension). Um 10% þeirra hafa hins vegar greindan háþrýsting vegna annarra undirliggjandi sjúkdóma svo sem sykursýki, nýrnasjúkdóma, skjaldkirtilssjúkdóma eða æðasjúkdóma (collagen vascular diseases) (26). Offita, kynþáttur (African-American) og hækkaður aldur eru helstu áhættuþættir kvenna á barneignaraldri fyrir því að greinast með langvinnan háþrýsting (5).

Hvað veldur meðgöngueitrun er ekki vitað með vissu en talið er að þar sé á ferðinni flókið samspil fylgju, ástands móður (t.d offita, sykursýki og háþrýstingur) og ýktra aðlögunarþátta líkamans á meðgöngu (27). Rannsóknir hafa leitt í ljós að helstu áhættuþættir fyrir meðgöngueitrun eru meðal annars fyrri saga um meðgöngueitrun, fyrsta meðganga, offita, fjölskyldusaga um meðgöngueitrun, fjölburameðganga og undirliggjandi langvinnir sjúkdómar svo sem háþrýstingur og sykursýki (28). Rannsakendur hafa sýnt fram á áhrif faðernis á líkur þess að kona fái meðgöngueitrun. Þessi tengsl virðast þó hverfa þegar leiðrétt er fyrir áhrifum tímalengdar milli meðgangna, þar sem lengri tími milli meðgangna eykur líkurnar á meðgöngueitrun (29). Erfðafræðilegur þáttur meðgöngueitrunar hefur verið rannsakaður á síðustu árum. Cnattingius og félagar komust að því, með rannsókn sinni á

sænskum konum, að í um helmingstilfella megi meðgöngueitrun rekja til erfðafræðilegra þátta. Þeirra niðurstöður benda jafnframt til þess að sameiginleg áhrif erfðafræðilegra þátta fóstursins og áhrif foreldra eru jafn mikilvæg og erfðafræðilegir þættir móður (30). Boyd og félagar skoðuðu tengsl erfða og persónulegra þátta við meðgöngueitrun hjá dönskum konum. Þeirra niðurstöður benda til þess að erfðir spili stærra hlutverk í meðgöngueitrun sem kemur fram snemma á meðgöngu en meðgöngueitrun sem kemur fram seint á meðgöngu (31). Niðurstöður rannsókna á síðari árum benda einmitt til þess að mismunandi orsakir og horfur séu eftir því hvort meðgöngueitrun greinist snemma eða seint á meðgöngunni. Valensise og félagar vilja skilgreina þetta sem tvo mismunandi sjúkdóma. Meðgöngueitrun sem greinist fyrir 34. viku telja þau að tengist óeðlilegri fylgjumyndun sem leiði til óæskilegra áhrifa á verðandi móður og vaxtarseinkunar fósturs. Meðgöngueitrun sem kemur fram á seinni hluta meðgöngu telja þau að rekja megi til ástands móður (32).

Meðgöngueitrun er mun algengari hjá frumbyrjum en fjölbyrjum (33). Stór (n=763,795) framsýn ferilrannsókn sem byggði á gögnum sænsku Fæðingaskrárinnar styður það. Þar voru 4,1% frumbyrja og 1,7% fjölbyrja greindar með meðgöngueitrun. Þær konur sem ekki höfðu haft meðgöngueitrun á fyrstu meðgöngu voru jafnframt mun ólíklegri til að fá meðgöngeitrun á næstu meðgöngu þó svo allt að átta ár væru á milli meðgangna. Niðurstöður rannsóknarinnar leiddu jafnframt í ljós að þær konur sem höfðu sögu um meðgöngeitrun sem greindist snemma á meðgöngunni voru líklegri til að fá meðgöngueitrun á næstu meðgöngu en þær sem höfðu sögu um meðgöngeitrun sem greindist seint á meðgöngunni. Þessar konur voru jafnframt líklegri til að fara í gegnum færri meðgöngur (34).

Meðgönguháþrýstingur og meðgöngueitrun eru mjög tengdir sjúkdómar sem hafa marga sameiginlega áhættuþætti. Báðir þessir sjúkdómar geta aukið áhættuna á alvarlegum fæðingarútkomum, þó áhættan sé meiri ef meðgöngueitrun er til staðar (24).

Bateman og félagar skoðuðu gögn frá 1999-2008 úr gagnagrunni (NHANES) sem er heilsufarskönnun (þversniðsrannsókn) í Bandaríkjunum. Niðurstöður þeirra sýndu að algengi háþrýstingssjúkdóma á meðgöngu var tiltölulega svipuð á milli ára, á þessu 10 ára tímabil eða um 8% (5). Roberts og félagar gerðu samanburðarrannsókn þar sem borin var saman tíðni greininga á háþrýstingssjúkdómum á meðgöngu í Skotlandi, Svíþjóð, Danmörku, Noregi, Ástralíu, Kanada og einu ríki Bandaríkjanna (Massachusetts). Við rannóknina var stuðst við heilsufarsskrár frá árunum 1997-2007. Sú rannsókn leiddi í ljós að dregið hafði úr greiningum á háþrýstingssjúkdómum á meðgöngu í norður Evrópu og Ástralíu á sama tíma og meðgöngulengd styttist og fleiri konur voru meðhöndlaðar fyrirbyggjandi. Í Massachusetts í Bandaríkjunum var þessu öfugt farið, greiningum á háþrýstingssjúkdómum hafði fjölgað sem þau leiða líkum að sé vegna breyttra greiningarskilmerkja (35). Í nýlegri rannsókn skoðuðu Ananth og félagar tíðni meðgöngueitrunar í Bandaríkjunum á árunum 1980-2010. Þau notuð upplýsingar úr 120 milljón fæðingaskrám. Þeirra niðurstöður sýndu aukna tíðni meðgöngueitrunar í Bandaríkjunum, var 3,4% árið 1980 en 3,8% árið 2010. Þessi aukning var drifin áfram af aukinni tíðni alvarlegrar meðgöngueitrunar, fór úr 0,3% árið 1980 í 1,4% árið 2010. Mögulegar ástæður nefna þau breytingar á lífsháttum, þá helst aukningu á offitu og að dregið hefur úr reykingum. Breytt greiningarskilmerki og aukið eftirlit hafa væntanlega líka áhrif (36).

1.2 Offita á meðgöngu

Í Bandaríkjunum eru 34% kvenna á aldrinum 20-39 ára offeitar og 59,5% eru annað hvort offeitar eða í yfirþyngd (37). Á Íslandi, líkt og annars staðar í heiminum, hefur orðið mikil aukning á offitu meðal kvenna og árið 2007 voru um 24% íslenskra kvenna offeitar (10). Ekki hafa verið gerðar margar rannsóknir á algengi offitu meðal kvenna á meðgöngu. Chu og félagar gerðu rannsókn á algengi offitu á meðgöngu meðal kvenna í nokkrum fylkjum Bandaríkjanna og komust að því að ætla megi að ein að hverjum fimm konum sé offeit á meðgöngu, í sumum fylkjum var hlutfallið jafnvel hærra eða allt að einni af hverjum þremur (38). Rannsóknir hafa tengt offitu á meðgöngu við ýmsa sjúkdóma á meðgöngu sem og vandamál í fæðingu. Þá er talið að offita á meðgöngu geti haft óhagstæð áhrif á fóstrið. Í lýðgrundaðri ferilrannsókn sem gerð var á öllum konum (n=369,347) sem fæddu barn í Danmörku á árunum 2004-2010 kom í ljós að þær konur sem voru í yfirþyngd og offeitar voru mun líklegri en konur sem voru í kjörþyngd til að til að; fá meðgöngusykursýki (odds ratio [OR] = 3,7-11), meðgöngueitrun (OR = 1,9-4,4), fara í keisaraskurð og þá sérstaklega bráðakeisaraskurð (OR = 1,2-2,1), fæða stórt barn (>4500gr) (OR = 1,6-2,7), eignast barn sem skoraði lágt á Apgar (OR = 1,3-1,9) og fæða andvana barn (OR = 1,4-1,9). Gagnlíkindahlutföllin (OR) jukust með hækkandi LÞS (39). Þessar niðurstöður eru í takt við niðurstöður annarra rannsókna (40, 41). Niðurstöður fyrri rannsókna hafa bent til þess að konur sem eru offeitar eða í yfirþyngd séu líklegri til að fæða fyrirbura (fyrir 37. viku). McDonald og félagar tóku saman niðurstöður 84 rannsókna á tengslum yfirþyngdar og offitu við fyrirburafæðingar og sýndu fram á þessa auknu áhættu á fyrirburafæðingum (42). Parker og félagar bentu á í nýlegri rannsókn að fyrri rannsóknir hafi ekki tekið tillit til þess hvort þessar fyrirburafæðingar væru sjálfkrafa fæðingar eða komið af stað með lyfjum. Þeirra niðurstöður sýna að offita á meðgöngu sé tengd aukinni áhættu á fyrirburafæðingum sem komið er af stað með lyfjum en ekki sjálfkrafa fyrirburafæðingum. Þau benda jafnframt á að háþrýstingssjúkdómar og meðgöngusykursýki séu helstu ástæður þess að fæðingu er komið af stað fyrir tíma (43).

En offita hefur ekki eingöngu áhrif á meðgönguna sjálfa. Hár LÞS fyrir meðgöngu eykur jafnframt líkur á fósturlátum snemma á meðgöngu sem og endurteknum fósturlátum (44, 45).

1.3 Offita og háþrýstingssjúkdómar á meðgöngu

Bateman og félagar skoðuðu helstu áhættuþætti fyrir háþrýstingi meðal kvenna á barneignaraldri í Bandaríkjunum á árunum 1999-2008 (5). Niðurstöður þeirra sýndu að offita var sá áhættuþáttur sem sem vóg þyngst á metunum. Konur sem voru með LÞS 30 - 35 voru fjórfalt líklegri til að fá háþrýsting en konur í kjörþyngd og konur með LÞS >35 voru sexfalt líklegri til að fá háþrýsting. Rannsóknir á áhrifum offitu á meðgöngu hafa að mestu einblínt á líkurnar á því að fá meðgöngeitrun. Bodnar og félagar sýndu fram á það í framsýnni ferilrannsókn að konur með LÞS = 30 væru um þrefalt líklegri til að fá meðgöngueitrun en konur með LÞS = 21 og aukast líkurnar með hækkandi LÞS (46). Þau benda á að með því að létta sig minnkar ofþung/offeit kona líkurnar á því að fá meðgöngueitrun. Í yfirlitsgrein sem tók til 13 ferilrannsókna sem tóku til samtals 1,4 milljón kvenna var reiknað út áhættuhlutfallið (risk ratio [RR]) milli kvenna með hæsta LÞS og kvenna með lægsta LÞS í hverri rannsókn. Áhættan fyrir meðgöngueitrun tvöfaldaðist yfirleitt við hverja 5-7 kg/m^2 hækkun á LÞS (47).

Langvinnur háþrýstingur er ástand sem á sér stað fyrir meðgöngu þar sem offita er einn af aðal áhættuþáttunum ásamt kynþætti og aldri (5, 25). Langvinnur háþrýstingur hefur aukist einna mest af þeim háþrýstingssjúkdómum sem Kuklina og félagar skoðuðu í rannsókn sinni (16). Þær konur sem eru með hækkaðan blóðþrýsting áður en meðganga hefst eru mun líklegri til að fá meðgöngueitrun en þær sem hafa eðlilegan blóðþrýsting (25). Séu konurnar hins vegar meðhöndlaðar með blóðþrýstingslyfjum fyrir meðgöngu minnka líkurnar á háþrýstingssjúkdómum á meðgöngu (15).

1.4 Reykingar á meðgöngu

Reykingar þungaðra kvenna hafa verið tengdar við alvarleg vandamál á meðgöngu og í fæðingu. Þar má nefna vaxtarseinkun fósturs, fylgjulos, lága fæðingarþyngd og fyrirburafæðingu (48, 49). Skaðleg áhrif reykinga móðurinnar á ófætt barnið má rekja til margra þátta, þar á meðal óbeinna áhrifa s.s lélegs næringarástands móður vegna lystarleysis sem níkótínið veldur, kolmónoxíð-útsetningar og lélegs blóðflæðis til fylgjunnar vegna æðasamdráttar sem kemur til vegna áhrifa katekólamína sem losna við nikótínörvun á nýrnahettur og taugafrumur. Þar við bætast bein áhrif nikótín asetýlkólín viðtaka sem verða til í heila fósturs mjög snemma á fósturskeiði (50). Dregið hefur úr reykingum í vestrænum löndum á síðustu árum (6). Sú þróun hefur jafnframt átt sér stað hjá konum á meðgöngu. Á árunum 2000-2005 fækkaði þeim sem reykja á meðgöngu úr 15,2% í 13,8% meðal bandarískra kvenna (51). Þrátt fyrir að skaðleg áhrif reykinga á meðgöngu hafi lengi verið vel þekkt þá benda niðurstöður rannsókna til að minnihluti kvenna sem reykti fyrir þungun hafi hætt að reykja á meðgöngu. Þar má nefna niðurstöður kanadískrar rannsóknar, sem birtar voru árið 2000, sýndu að um 70% þeirra kvenna sem reyktu við upphaf meðgöngu gerðu það enn þegar kom að fæðingu (52). Nýlegri gögn frá Bandaríkjunum sýndu að um 45% þeirra kvenna sem reyktu þrem mánuðum fyrir meðgöngu hættu að reykja á meðgöngunni (51). Mögulega gefa þessar niðurstöður til kynna að hlutfall kvenna á vesturlöndum sem hættir að reykja á meðgöngu fari vaxandi.

1.5 Reykingar og háþrýstingssjúkdómar á meðgöngu

Skaðsemi reykinga fyrir móður og barn á meðgöngu er vel þekkt. Hammoud og félagar skoðuðu tengsl reykinga við ýmis vandamál tengd meðgöngu og fæðingu (49). Rannsóknin tók til 29 fæðingardeilda í Þýskalandi á árunum 1991-1997 og unnið var með gögn frá um 170 þúsund fæðingum. Þeirra niðurstöður sýndu að áhættan fyrir meðgöngueitrun var í öfugu hlutfalli við fjölda reyktra sígarettna á dag. Eftir að hafa leiðrétt fyrir mögulegum blöndunarþáttum bentu niðurstöður til þess að reykingar drægju úr líkunum á því að fá meðgöngueitrun (OR= 0,64, 95% CI 0,59-0,70). Jafnframt kom í ljós að með því að auka fjölda sígarettna um fimm á dag minnkaði áhætta meðgöngueitrunar um 18%. Þessar niðurstöður eru samhljóma niðurstöðum annarra rannsókna (53).

Norsk rannsókn sem gerð var á um 100 þúsund konum á árunum 1999-2008 tekur í sama streng (54). Konurnar svöruðu spurningalista varðandi reykingasögu tvisvar sinnum á meðgöngunni og fengnar voru upplýsingar um fæðingaútkomur úr Fæðingaskrá. Um 23% þessara kvenna reyktu við upphaf meðgöngu en fjöldi þeirra sem reykti á síðasta hluta meðgöngunnar var aðeins 8%. Þær konur sem sögðust hafa hætt að reykja fyrir síðasta þriðjung meðgöngunnar voru nánast jafn líklegar til að fá

meðgöngueitrun eða meðgönguháþrýsting og þær konur sem sögðust ekki reykja. Þær konur sem svöruðu að þær hefðu reykt samfellt út alla meðgönguna höfðu mesta áhættuminnkun.

Flestar rannsóknir hafa sýnt fram á verndandi áhrif reykinga á meðgöngu fyrir meðgöngueitrun en rannsókn Engel og félaga sýnir svipaða verndun fyrir meðgönguháþrýsting (54). Ástæður verndandi áhrifa reykinga fyrir meðgöngueitrun og meðgönguháþrýsting eru óþekktar. Ýmsar getgátur hafa þó verið á lofti. Líklega er það eitthvað í sígarettubrunanum sem hefur þessi verndandi áhrif. Niðurstöður rannsóknar Wikström og félaga á mismunandi áhrifum neftóbaks (snus) og sígarettna, þar sem nikótín er sameiginlegt innihaldsefni, benda til þess að notkun á neftóbaki sé ekki verndandi fyrir meðgöngueitrun og meðgönguháþrýsting líkt og reykingar (53). Pipkin og félagar hafa sýnt fram á að þótt reykingar séu verndandi fyrir meðgöngueitrun geta þær haft neikvæð áhrif á fæðingarútkomur þeirra kvenna sem reykja og fá meðgöngueitrun. Þær voru tvöfalt líklegri til að fæða fyrir 34. viku (OR=1,98) og líklegri til að fæða barn með neikvæðri fæðingarútkomu (OR=1,87). Þær voru jafnframt fimmfalt líklegri til að fá fæðingarkrampa (eclampsia) en þær konur sem reyktu ekki (OR=4,88). Niðurstöður Pipkin og félaga sýna að ef reykingakona fær meðgöngeitrun eru hún mun líklegri til að fá alvarlegri einkenni sem koma jafnframt fyrr með alvarlegum afleiðingum fyrir móður og barn og því mikilvægt að hún hætti að reykja (55).

1.6 Samþætt áhrif reykinga og offitu á háþrýstingssjúkdóma á meðgöngu

Engin heildstæð rannsókn hefur verið gerð á tengslum líkamsþyngdarstuðuls og reykinga á meðgöngu við háþrýstingssjúkdóma meðal þungaðra kvenna á Íslandi. Jafnframt er almennt lítið vitað um samvirkniáhrif hás líkamsþyngdarstuðuls og reykinga á háþrýstingssjúkdóma meðal barnshafandi kvenna í alþjóðlegu samhengi umfram að áhætta eykst með háum LÞS en minnkar með reykingum.

Þær fáu rannsóknir sem þó hafa verið gerðar eru ekki samhljóma um samþætt árif líkamsþyngdar og reykinga. Ness og félagar skoðuðu niðurstöður úr stórri framsýnni ferilrannsókn (n=55,908) sem gerð var á árunum 1959-1965 í Bandaríkjunum (56). Á þessum tíma var einmitt mun algengara að konur reyktu á meðgöngu en rúmlega helmingur þessara kvenna reykti á meðgöngunni og var meðgöngueitrun sjaldgæfari í þeim flokki, þ.e. kvenna sem reyktu. Eftir að útiloka konur með undirliggjandi sjúkdóma (t.d langvinnan háþrýsting), fjölbyrjur og fjölburafæðingar stóðu eftir gögn um 7757 konur. Borið saman við konur í kjörþyngd voru reykingar verndandi fyrir konur í undirþyngd (OR=0,54 og OR=0,24 fyrir stóreykingakonur). Ness og félagar fundu ekki verndandi áhrif reykinga hjá konum í yfirþyngd/offitu (OR=1,04 og OR=0,8 fyrir stórreykingakonur; *p*=0,4) (56). Niðurstöður Stone og félaga eru hins vegar ekki á sama máli. Þeir gerðu lýðgrundaða aftursýna ferilrannsókn á konum í Missouriríki í Bandaríkjunum og byggðu rannsókn sína á upplýsingum úr fæðingarvottorðum. Rannsóknin náði alls til 129,674 kvenna. Þeirra niðurstöður sýndu að líkurnar á því að fá meðgöngueitrun voru lægri hjá þeim sem reykja burtséð frá því hver líkamsþyngdarstuðullinn var fyrir meðgöngu. Áhættuhlutfall (RR) var svipað fyrir alla flokka LÞS, RR = 0.8 fyrir kjörþyngd, RR = 0.72 fyrir ofþyngd, RR = 0.84 fyrir offitu og RR = 0.71 fyrir mikla offitu (57). Ness og félagar gagnrýndu þessar niðurstöður og bentu á að upplýsingar um reykingar og meðgöngueitrun væru ekki mjög áreiðanlegar á fæðingarvottorðum og því líklegt að rangflokkun hafi átt sér stað í rannsókn Stone og

félaga. Jafnframt gagnrýndu þeir að ekki hafi verið sýnt fram á samband reykinga og meðgöngueitrunar lagskipt eftir LÞS í aðlöguðu fjölbreytulíkani.

Niðurstöður flestra rannsóknir eru þó samhljóma um að þrátt fyrir verndandi áhrif reykinga á meðgöngueitrun og meðgönguháþrýsting geta þær líkt og hár líkamsþyngdarstuðull, haft skaðleg áhrif á móður og barn á meðgöngu (49).

2 Markmið

Markmið þessarar rannsóknar er að skoða tengsl líkamsþyngdarstuðuls (LÞS) og reykinga á meðgöngu við háþrýstingssjúkdóma meðal þungaðra kvenna á Íslandi. Jafnframt að skoða samþætt áhrif LÞS og reykinga á áhættu þess að greinast með háþrýstingssjúkdóm á meðgöngu. Nánar tiltekið prófum við eftirfarandi tilgátur í völdu úrtaki (nested in a cohort study) allra fæðinga á Landspítala Háskólsjúkrahúsi á árunum 1989-2004:

- Að teknu tilliti til bakgrunnsþátta eru konur með líkamsþyngdarstuðul sem er hærri en 25 líklegri en konur með líkamsþyngdarstuðul lægri en 25 til að fá háþrýstingssjúkdóma á meðgöngu.

- Að teknu tilliti til bakgrunnsþátta eru konur sem reykja síður líklegar til að fá háþrýstingssjúkdóma á meðgöngu samanborið við konur sem reykja ekki.

- Að sambandið milli líkamsþyngdarstuðuls og háþrýstingssjúkdóma á meðgöngu sé sterkara meðal kvenna sem reykja en þeirra sem ekki reykja.

Samkvæmt þriðju tilgátunni gerum við ráð fyrir að reykingar hafi ekki verndunaráhrif fyrir háþrýstingssjúkdómum hjá offeitum konum, jafnvel þótt áður hafi verið sýnt fram á verndunaráhrif reykinga almennt séð. Við gerum því ráð fyrir að offeitar konur séu, samanborið við konur sem eru í kjörþyngd, í aukinni áhættu fyrir háþrýstingssjúkdómum óháð því hvort þær reykja eða ekki.

Jafnframt áætlum við að skoða ofangreind sambönd milli líkamsþyngdarstuðuls, reykinga og háþrýstingssjúkdóma á meðgöngu með þrepaflokkun á líkamsþyngdarstuðli.

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Grein

Verður send til birtingar í *American Journal of Obstetrics and Gynecology*

Title Page - Original Research

Body Mass Index, Smoking and Hypertensive Disorders during Pregnancy: A Population based Case-Control Study

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Disclosure statement: The authors reports no conflict of interest.

Financial support: This study was supported financially by Icelandic Centre for Research, START - Reintegration fellowship (#130814-051). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The authors did not receive financial support from any other organization for the submitted work.

Abbreviations

BMI: body mass index

CI: confidence interval

OR: odds ratio

HTD: hypertensive disorder

SBP: systolic blood pressure

DBP: diastolic blood pressure

ICD-10: International classification of diseases, 10th revision

Word count abstract: 300

Word count main text: 3681

Condensation and Short Version of Title

Short Title: BMI, Smoking and Hypertension Disorders of Pregnancy

Condensation: Overweight and obese women are at considerably increased risk for all types of hypertensive disorders during pregnancy, this risk is enhanced even further with smoking.

Abstract Page

Key Words: body mass index; hypertension, pregnancy-induced; obesity; pre-eclampsia; smoking

ABSTRACT

Objective: The purpose of this study was to investigate the association of smoking and body mass index with hypertensive disorders during pregnancy, including pre-existing hypertension, gestational hypertension and preeclampsia. Further, to assess potentially combined effects of high body mass index and smoking on these disorders.

Study design: A case-control study based on national registers, nested within all pregnancies in Iceland 1989-2004, which resulted in birth at the Landspitali University Hospital. A total of 500 women were included as cases and 1000 as controls; matched on year of childbirth (1:2) and restricted to women with no registered diagnoses of pre-existing or gestational diabetes. Cases had a registered hypertensive disorder anytime during pregnancy (International Classification of Disease, 10^{th} Revision, codes O10-16) and no registered diagnosis of gestational or pre-existing diabetes. Body mass index (kg/m^2) was based on early pregnancy height and weight measures. Adjusting for potential confounders, we used logistic regression models to calculate odds ratios (OR), and corresponding 95% confidence intervals (CI), as measures of association. Analyses were conducted stratified by smoking status and preterm births using the Mantel-Haenzel method.

Results: Women's body mass index during early pregnancy was associated with all types of hypertensive disorders during pregnancy (pre-existing hypertension, gestational hypertension and preeclampsia). Compared with normal weight women,

the multivariable adjusted OR for any hypertensive disorder was 1.8 (95% CI 1.3-2.3) for overweight women and 3.1 (95% CI 2.2-4.3) for obese women. The OR for any hypertensive disorder with obesity was higher among smokers (OR=3.9, 95% Cl 1.8-8.6) than non-smokers (OR=3.0, 95% CI 2.1-4.3).

Conclusion: Overweight and obese women are at considerable risk for all types of hypertensive disorders during pregnancy as compared with normal weight women. This risk is enhanced even further with smoking, despite the established inverse association of smoking with preeclampsia and other hypertensive disorders of pregnancy.

Main Text

INTRODUCTION

Hypertensive disorders, including chronic hypertension, gestational hypertension, and preeclampsia, occur in approximately 6-8% of all pregnancies[1] and are a significant source of maternal and fetal morbidity.[2] As the prevalence of advanced maternal age[3,4] and obesity[5] increase among childbearing women in Western countries, hypertensive disorders are likely to become increasingly common obstetric conditions. Compared with offspring of normal pregnancies, offspring of preeclamptic pregnancies have a 1.5-to 2-fold increased risk of perinatal or infant mortality. Approximately a third of babies born after a preeclamptic pregnancy are growth restricted, and preeclampsia is responsible for 15% of all preterm births.[6]

While obesity is a known risk factor for preeclampsia and other hypertensive disorders,[7] smoking during pregnancy has been shown to have a protective effect on the development of preeclampsia.[8] There are relatively few data regarding the interacting effects of these two lifestyle-related factors on these common pregnancy conditions.[9] To what extent maternal smoking and body mass index interact in the development of preeclampsia and other hypertensive disorders during pregnancy is not well established.

We aimed to examine the association between smoking, BMI and hypertensive disorders, including preeclampsia, gestational hypertension and pre-existing hypertension, during pregnancy, taking in account demographic and pregnancy related factors. Further, to assess potentially interacting effects of smoking and BMI on hypertensive disorders among pregnant women.

MATERIALS AND METHODS

Study Design

We conducted a case-control study nested within all pregnancies in Iceland 1989-2004, which resulted in birth at the Landspitali University Hospital. The study was based on data from the National Medical Birth Registry and maternity records linked via women's unique personal identification number.

Health care is universal and publicly funded in Iceland. Prenatal care is offered in a uniform manner at local clinics every two to four weeks of pregnancy (10 visits for nulliparous women and 7 visits for others), with the first prenatal visit occurring around week 10. Women which need specialized care get more follow up.[10] The Landspitali University Hospital provides secondary and tertiary services for the whole of Iceland. It covered approximately 2900 births annually during the study period,[11,12] including mainly deliveries among mothers residing in the capital area (Table 1), as well deliveries among mothers in need of specialized medical care.

Ascertainment of Cases and Controls

As cases we randomly selected a total of 500 women from the electronic National Medical Birth Registry with any registered hypertensive disorder of pregnancy (International Classification of Disease, 10th Revision [ICD-10] [13]codes, O10-16) and no diagnosis of diabetes (ICD-10 codes, O24, E08-13). Hypertensive disorders of pregnancy were further categorized as: *pre-existing hypertension* (O10), *gestational hypertension* (O13, O16) and *preeclampsia* (O14, O15, O11). Preeclampsia superimposed on pre-existing hypertension (O11) was included with preeclampsia, as only four such cases were identified. No cases of gestational edema and

proteinuria without hypertension (O12) were identified. According to the diagnostic criteria,[14] *pre-existing hypertension* is defined as hypertension that is present and observable before pregnancy or that is diagnosed before the 20th week of pregnancy; *gestational hypertension* and *preeclampsia* usually occur after pregnancy week 20.

To evaluate the accuracy of the diagnosis of hypertensive disorders in the National Medical Birth registry, we obtained blood pressure values (systolic and diastolic) from maternity records for each woman, as measured at first and last prenatal visit. We then conducted linear regression models, adjusting for parity, multiple gestation and maternal age, to compare mean blood pressure values by diagnosis and assess diagnostic plausibility.

As controls we selected a total of 1000 women Medical Birth Registry, matched with cases (1:2) on year of childbirth, who had no registered diagnosis of a hypertensive disorder of pregnancy or diabetes.

Measures of Body Mass Index and Smoking

Information on measured weight, height and self-reported smoking behavior during pregnancy was manually retrieved from maternity records. Weight (kg) and height (m) are measured at the first prenatal visit for each pregnant woman (before week 15 for 80% of pregnancies in the study population). Body mass index (BMI) was defined and categorized in accordance with international standards[15] as kg/m^2: *underweight* (BMI < 18.5) *normal weight* (BMI 18,5-24,9), *overweight* (BMI 25-29,9), *obese* (BMI ≥ 30). BMI was available for 1445 (96.3%) of the study population, i.e. 483 (96.4%) of cases and 962 (96.3%) of controls.

Smoking behavior was self-reported during prenatal visits and categorized as: *non-smoker*, *smoker* and *discontinued smoker* (smoked during early pregnancy but quit). Information on smoking was not available for 21 women. In the analyses we further dropped discontinued smokers because of low frequencies (n=41) and uncertainty of when smoking had been discontinued. Information on quantity or type of smoking was not available. Data on smoking status was thus analyzed for 1383 (95.7%) of the 1445 women with available BMI.

Covariates

Additionally, we obtained information on women's demographic and pregnancy related characteristics from the National Medical Birth Registry, including maternal age during pregnancy, nationality, residency, and cohabitation with other parent, parity, multiple gestation and gestational length. The study population was restricted to women without a registered diagnosis of diabetes, clinical guidelines for the diagnosis and treatment of gestational diabetes evolved considerably during the time study until uniform screening initiated in the late 1990s[16] in Iceland. Other registered maternal conditions, such as renal diseases (ICD10 codes N00-N99, Q61, O27.1), collagen vascular diseases (ICD codes L93, L94) and endocrine disorders (ICD-10 codes E00-E90) were assessed but not used covariates because of too few observations. Pregnancies were considered preterm if they lasted < 37 weeks and as full-term if ≥ 37 weeks.

Data analysis

Of 1500 unique personal identification numbers extracted, records were incomplete or unavailable for three women and data on BMI missing for another 52 women; resulting in a population of 1445 women (483 cases, 962 controls) available for the main data analysis. Analyses in which smoking status was included contained a total of 1383 women after exclusion of those with missing values (n= 21) and discontinued smoking (n=41).

We first calculated the crude odds, odds ratios (OR) and corresponding 95% confidence intervals (CI), as measures of association of hypertensive disorders of pregnancies (any; pre-existing hypertension, gestational hypertension, preeclampsia) separately with BMI groups (normal weight, overweight, obese) and smoking status (no, yes). With logistic regression models we then adjusted for all available covariates (women's age, nationality, residency, cohabitation, working status, parity and multiple gestation) simultaneously by using a backward selection of covariates and Yates continuity corrections.[17] The final models included only maternal age, parity and multiple gestation, as these were the only covariates which significantly affected the measured associations. Analyses of association between BMI groups and each hypertensive outcome were conducted stratified by smoking status and preterm pregnancy using Mantel-Haenzel method.[18]

In a supplementary analysis we attempted to evaluate the accuracy of the registration of hypertensive disorders by comparing blood pressure values (systolic and diastolic) between diagnostic groups. To this end we conducted linear regression models estimating mean blood pressure values within each diagnostic group and adjusted for parity, multiple gestation and maternal age.

All analyses were performed using Excel spreadsheets and R statistical software for computing.[19] The study was approved by the Icelandic National Bioethics Committee (VSNb2012040011/03.07) and the Data Protection Authority (2012050619AT/-).

RESULTS

Demographic and pregnancy characteristics of women with hypertensive disorders during pregnancy (cases) and matched controls (no hypertensive disorders) are detailed in Table 1. We display the characteristics only for women with known BMI values (N=1445); measures of either height or weight were unknown for n=18 cases (3.6%) and n=37 (3.7%) controls. The characteristics of those women with missing BMI and known BMI were largely similar except for nationality. Those with missing BMI were more likely to be non-Icelandic. The demographic characteristics of cases and controls were largely similar, but they differed in parity. Hypertensive cases were more likely than controls to be nulliparous (59% vs. 38%), and they were also slightly younger than the controls (28.2 vs. 28.5 years).

Of the 1445 women, 17.9% (n=259) reported smoking during pregnancy, another 2.8% (n=41) reported discontinued smoking during pregnancy and 1.5% (n=21) had an unknown smoking status. The discontinuers were excluded from all analyses as we were unable to assess when exactly they had quit smoking.

The mean blood pressure values (systolic and diastolic) by diagnosis are detailed in Figure 1 and supplementary table 2). After adjusting for parity, multiple gestation and maternal age the mean blood pressure values, in the final visits, was higher for the hypertensive diagnosis compared with the control group.

The odds of being diagnosed with a hypertensive disorder during pregnancy were lower for smokers than non-smokers (21.2% vs. 13.9%); with a crude odds ratio of 0.60 (95% CI 0.44-0.82). Adjusting for parity, multiple gestation, maternal age or any other available covariate did not affect the effect estimate ($OR_{adjusted}$=0.60, 95% CI 0.44-0.82). We found a reverse association of smoking with each of the separate hypertensive outcomes but the protective effect sizes differed; preeclampsia (OR_{crude} = 0.71, 95% CI 0.50-0.99; $OR_{adjusted}$ = 0.68, 95% CI 0.47-0.96), gestational hypertension (OR_{crude} = 0.34, 95% CI 0.13-0.74; $OR_{adjusted}$ = 0.31, 95% CI 0.13-0.75)) and pre-existing hypertension (OR_{crude} = 0.51, 95% CI 0.25-0.93; $OR_{adjusted}$ = 0.53, 95% CI 0.26-0.97).

According to measured height and weight at around 13 weeks of pregnancy, 1.7% (n=24) of the 1445 women was underweight, 57.4% (n=829) were normal weight, 26.0% (n=376) overweight and 14.9% (n=216) were obese. We collapsed the underweight women with the normal weight group in all analyses.

The associations of BMI and hypertensive disorder during pregnancy are detailed in Table 2. Compared with normal weight women, both overweight and obese women had higher odds of any hypertensive disorders during pregnancy. The crude odds ratio for any hypertensive disorder was 1.63 (95% Cl 1.26-2.11) for overweight women and OR = 2.79 (95% Cl 2.05-3.80) for obese. Adjusting for parity, multiple gestation and maternal age amplified positive effect estimates somewhat (Table 2). We found positive associations of BMI with each separate hypertensive outcome (preeclampsia, gestational hypertension and pre-existing hypertension). In comparison to normal weight women, the odds of preeclampsia and gestational hypertension increased by 1.7-fold for overweight women and by 2.4- to 3-fold for obese women, with effect estimates slightly higher when adjusting for parity, multiple

gestation and maternal age (Table 2). The adjusted odds ratios were highest for pre-existing hypertension; 1.8 and 5.4 among overweight and obese women, respectively, compared with normal weight women. Only maternal age seemed to affect the association between BMI and pre-existing hypertension, by slightly attenuating the estimates (Table 2).

We conducted stratified analyses to evaluate whether the association between BMI and hypertensive disorders during pregnancy varied by women's smoking status (Table 3). Among smokers the odds for any hypertensive disorder increased by almost 4-fold (OR = 3.91, 95% Cl 1.78-8.59), comparing obese with normal weight women. Among non-smokers it increased 2.98-fold (95% Cl 2.07-4.31) for obese women. The effect estimates stratified by smoking status were of similar magnitude for preeclampsia (Table 3), but we lacked statistical power to meaningfully evaluate the association of BMI with gestational hypertension and pre-existing hypertension.

Hypertensive cases were more likely to deliver preterm than non-hypertensive controls (18.6% vs. 7.4%). We conducted stratified analysis to evaluate if the association between BMI and hypertensive disorders of pregnancy varied with gestational length. Among women with full-term pregnancies, the odds ratio for hypertensive disorder remained similar to the un-stratified estimates for both obese (OR = 3.78, 95% Cl 2.69-5.33) and overweight (OR=1.98, 95% Cl 1.48-2.66), comparing with normal weight women (Table 4). We did not have enough statistical power to meaningfully evaluate the association of BMI and hypertensive disorders in preterm pregnancies, although the effect estimates point to an attenuated association between BMI and hypertensive disorders before week 37 of pregnancy.

COMMENT

Main finding

The results of this population based case-control study indicate that overweight and obese women are, compared with women of normal weight, at increased risk of developing hypertensive disorders of pregnancy, including preeclampsia, pre-existing- and gestational hypertension. Importantly, the results suggest that overweight and obese women who smoke during pregnancy are at even further risk of developing these common conditions, even though smoking per se seems to be an independent protective factor for the hypertensive disorders of pregnancy. Our findings may help elucidate the complicated interplay of these lifestyle-related factors with the hypertensive disorders and potentially advance our understanding of their varying entities

Study strengths and limitations

The study was conducted over a 15-year period in Iceland, where women have equal access to prenatal care free of charge. Maternal care was provided at local health clinics at least 7-10 times during pregnancy and according to national guidelines.[10] The data originated from women who gave birth at the National University Hospital, where over 75% of all births in the country occurred.[11] The study strengths mainly lie in the homogeneous study population, uniform diagnostic- and health care system, which reduce residual confounding by factors such as socio-economic status and differential prenatal care.

Our study has several important limitations. First, we restricted the study population to women with no registered diagnosis of diabetes, since gestational diabetes is likely to have been under-detected in the country before the year 2000. As diabetes is

associated with both BMI,[20] smoking[21] and hypertensive disorders of pregnancy,[22] not being able to estimate how the condition might have affected the observed associations, limits the generalizability of our results. Second, the exact dates of hypertensive diagnoses were not available in our data, limiting our possibility to know if the hypertension had an early or late onset (i.e. before or after week 34 of pregnancy). However, as an attempt to approximate whether the effect of BMI varied by timing of disease onset, we stratified the data by preterm pregnancies and found the associations to hold mainly for full-term pregnancies. Third, although all diagnoses were based on ICD-codes, misclassification of disease status may still be a possibility. To evaluate the validity of the diagnoses we estimated adjusted mean blood pressure values, at the first and last prenatal visits, by diagnosis status and found these values to be in line with the expected blood pressure of each diagnosis. Fourth, our purpose was to record BMI measured in early pregnancy but for 80% of the women it was measured before week 15 of pregnancy. Thus, there is a possibility that some women were misclassified in BMI category. There were also some missing data on BMI, but we found otherwise little difference in the demographic and pregnancy characteristics of those women with known and unknown BMI. Finally, as smoking was self-reported some women may have misreported their status. We would expect such misreporting mainly to have been smokers classified as non-smokers, which would in turn have attenuated the observed difference of the estimated effect of BMI on hypertension between smokers and non-smokers (i.e. a more similar estimate of OR for smokers and non-smokers).

Interpretation

The risk increase we observed for hypertensive disorders during pregnancy was threefold among obese women and nearly two-fold among overweight women,

compared with normal weight women. Our results indicated a dose-response relation of BMI with each separate hypertensive outcome, i.e. preeclampsia, pre-existing and gestational hypertension. This is consistent with previous results found among pregnant women, although most have focused on the relationship with preeclampsia.[23,24] But as Bateman et al.[25] demonstrated, using nationally representative data from NHANES, obesity is an independent risk factor for hypertension among all women of reproductive age, with prevalence increasing in near linear fashion with BMI.

Consistent with the elevated risk for preeclampsia we observed among overweight (OR=1.7) and obese (OR=2.4) women in our data, Bodnar et al.[23] also found that pre-pregnancy BMI had a dose-dependent relation with preeclampsia, with a triple risk among women with a BMI of 30 compared with women who had a BMI of 21. These findings are in line with the results of a systematic review from 2003, including 13 cohort studies, that the risk of developing preeclampsia doubled for every 5-7 kg/m^2 increase in BMI.[26]

The positive relationship between BMI and gestational hypertension in our data was of similar magnitude as for preeclampsia. Most previous studies assessing BMI and gestational hypertension have analyzed it as a combined outcome with preeclampsia.[23,27] As the two hypertensive conditions have been shown to share many risk factors[28], the similar association of each with BMI is not of surprise. On the other hand, pre-existing hypertension and preeclampsia/gestational hypertension have independent entities.[14] While the latter generally occur after week 20 of pregnancy, pre-existing hypertension is by definition detected earlier. Several studies have, however, demonstrated these different entities to share at least one risk factor, namely obesity.[22,25] Our results concur with previous studies indicating that

overweight and obese women are more likely to have pre-existing hypertension.[25] But as BMI is likely to have been measured after the onset of pre-existing hypertension, it is difficult to ascertain high BMI as a definite causal risk factor in our data. Advanced age has also been considered in previous studies a risk factor for pre-existing hypertension.[25] After adjusting for age in our data the positive relationship between overweight/obesity and pre-existing hypertension remained, although slightly attenuated.

Smoking

In line with the previously established studied negative association between smoking and preeclampsia/gestational hypertension,[29-31] our data showed an odds ratio close to 0.6 after adjustments – indicating the protective effect of smoking on the disorders. But how does smoking affect the observed increase in risk for hypertensive disorders among overweight/obese women? In our data we found that women who smoked in addition to being overweight, or especially obese, were at an even higher risk, than those who did not smoke. This pattern was obvious for preeclampsia and pointed to a similar direction for gestational hypertension or pre-existing hypertension, but we lacked statistical power to draw sound conclusions for the latter two outcomes. Previous studies have shown conflicting results on the combined effects of BMI and smoking on the hypertensive outcomes during pregnancy. Stone et al. [32] suggested in a retrospective study based on data from birth certificates, that smoking during pregnancy decreased the risk for preeclampsia regardless of women pre-pregnancy BMI. They examined the effect of smoking on preeclampsia stratified by BMI categories, while the main analysis of the current study was the association between BMI and hypertensive disorders stratified by smoking, which are not necessarily the same causal pathways. Ness et al.[33], on the other hand, presented in a large,

prospective study, that the protective effect of smoking was eliminated if a woman was obese. We found a similar pattern as Ness of a decreasing protective effect smoking on hypertensive disorders with increasing BMI in our supplementary analyses (data not shown), but the main study focus was on the varying effect of BMI according to smoking status.

Preterm Pregnancies

Previous findings suggest that women with preeclampsia are more likely to give birth preterm, than women with gestational hypertension, and that they are more likely to go through medically induced labor.[28] We attempted to approximate timing of disease onset by analyzing preterm and full-term birth separately. Our data suggested that overweight and obesity were especially associated with hypertensive disorders in full-term pregnancies. We were, however, not able draw sound conclusions for preterm pregnancies, but the estimates suggest that the effect of BMI on hypertensive disorders was less pronounced among preterm pregnancies. McDonald et al.[34] studied the relationship between obesity/overweight during pregnancy and preterm deliveries in a systematic review of 84 studies. Their findings showed that obese and overweight women were at increased risk of preterm birth and induced preterm birth. In a recent study Parker et al.[35] suggested that preterm births among obese women were related to their conditions and that these preterm births were more likely to be medically-induced than spontaneous. Further, they showed that hypertension and diabetes to be independent risk factors for medically induced preterm births. Similarly in our data, cases, i.e. women with hypertensive disorders, were more likely than controls to give births preterm.

Biological and causal mechanism

Hypertensive disorders during pregnancy have different epidemiological characteristics, pathophysiology and risks for mother and unborn child. In pre-existing hypertension elevated blood pressure is the cardinal pathophysiologic feature, whereas in preeclampsia increased blood pressure is important primarily as a sign of the underlying disorder.[14] Previous studies have linked hypertensive disorders during pregnancy with increased risk for chronic diseases for the women in the nearest future. This association is believed to be due to same risk factors as there are for hypertensive disorders during pregnancy and many chronic diseases.[36,37] As has been shown in the current and previous studies, smoking seems to protect women from developing hypertensive disorders during pregnancy. Our findings indicate that overweight/obese women which smoke are at increased risk for developing hypertensive disorders during pregnancy. This raises questions about something else affecting the causal pathway in this group of women. Smoking obese women might have some other risk factors which are affecting the causal pathway for example diet or social status. Preeclampsia is multi-organ syndrome and previous studies have suggested a different underlying causes of early and late onset of preeclampsia/gestational hypertension and even suggested two different disorders.[38] Late onset preeclampsia is more common (80%) than early onset (20%).[39] Early onset preeclampsia might be linked to abnormal placentation while late onset preeclampsia might be linked to maternal factors.[38,39] In a population based study Lisonkova and Joseph[40] did on singleton deliveries in Washington 2003-2008 results indicated that the consequences of early onset preeclampsia had greater adverse effects on the fetus and infant compared with late onset disease. So that the timing of onset is an important factor when predicting and treating

preeclampsia. Obesity is a crucial factor both in early and late onset preeclampsia.[24] In a study on the association of family and personal factors with preeclampsia Boyd et al.[41] findings suggest that early onset preeclampsia appears to have larger genetic component than late onset preeclampsia.

Final conclusion

In conclusion, our data indicate that obesity and overweight play a crucial role in relation to hypertensive disorders of pregnancy. A high BMI seems to considerably increase women's likelihood of hypertensive conditions during pregnancy and smoking increases this likelihood even further. Our findings warrant further investigation, especially in light of current and previous findings showing that independently smoking to be protective against hypertensive disorders of pregnancy.

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TABLES AND FIGURES

Table 1 – Demographic and Pregnancy Characteristics of Cases and Controls[a]

	Total N (%)	Cases n (%)	Controls n (%)	p-value
Total	1445 (100)	483 (100)	962 (100)	
Age, years				
mean	28.4	28.1	28.5	
< 25	409 (28.3)	157 (32.5)	252 (26.2)	0.008
25 - 34	793 (54.9)	238 (49.3)	555 (57.7)	
≥ 35	243 (16.8)	88 (18.2)	155 (16.1)	
Nationality				
Icelandic	1410 (97.6)	469 (97.1)	941 (97.8)	0.45
other	32 (2.2)	13 (2.7)	19 (2.0)	
missing	3 (0.2)	1 (0.2)	2 (0.2)	
Residency				
capital area	1087 (75.2)	355 (73.5)	732 (76.1)	0.3
non capital area	257 (17.8)	105 (21.7)	152 (15.8)	
missing	101 (7.0)	23 (4.8)	78 (8.1)	
Cohabitation				
lives with other parent	1238 (85.7)	412 (85.3)	826 (85.9)	0.81
single	205 (14.2)	70 (14.5)	135 (14.0)	
missing	2 (0.1)	1 (0.2)	1 (0.1)	
Working status				
paid work	1046 (72.4)	350 (72.5)	696 (72.3)	
homemaker, not working, disability	28 (1.9)	8 (1.7)	20 (2.1)	0.12
student	197 (13.6)	77 (15.9)	120 (12.5)	
other	174 (12.0)	48 (9.9)	126 (13.1)	
Parity, n				
0	659 (45.6)	285 (59.0)	374 (38.9)	<0.0001
1	436 (30.2)	102 (21.1)	334 (34.7)	
≥ 2	350 (24.2)	96 (19.9)	254 (26.4)	
Multiple gestation				
no	1348 (93.3)	437 (90.5)	911 (94.7)	0.004
yes	97 (6.7)	46 (9.5)	51 (5.3)	

Abbreviations: HTD, hypertensive disorder of pregnancy; p-value, Fisher Exact Test for difference in proportions between cases and controls.

[a] Cases and controls are matched on year of childbirth. All cases and controls are restricted to women without any registered diabetes during pregnancy.

Table 2 - Association of Body Mass Index with Hypertensive Disorders during Pregnancy

	Total N	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Any HTD	1445	483 (100)	962 (100)		
normal weight (BMI <24.9)	853	231 (47.8)	622 (64.7)	1	1
overweight (BMI 25-29.9)	376	142 (29.4)	234 (24.3)	1.63 (1.26-2.11)	1.75 (1.34-2.29)
obese (BMI ≥30)	216	110 (22.8)	106 (11.0)	2.79 (2.05-3.80)	3.08 (2.24-4.25)
Preeclampsia	1281	313	962		
normal weight (BMI <24.9)	786	161 (51.4)	622 (64.7)	1	1
overweight (BMI 25-29.9)	325	93 (29.7)	234 (24.3)	1.54 (1.14-2.06)	1.72 (1.26-2.34)
obese (BMI ≥30)	167	59 (18.9)	106 (11.0)	2.15 (1.49-3.08)	2.37 (1.62-3.46)
Gestational hypertension	1042	75	962		
normal weight (BMI <24.9)	660	35 (46.7)	625 (64.7)	1	1
overweight (BMI 25-29.9)	257	23 (30.7)	234 (24.3)	1.75 (1.00-3.01)	1.77 (1.00-3.09)
obese (BMI ≥30)	125	17 (22.7)	108 (11.0)	2.86 (1.51-5.23)	2.96 (1.55-5.47)
Pre-existing hypertension	1062	95	962		
normal weight (BMI <24.9)	660	35 (36.8)	622 (64.7)	1	1
overweight (BMI 25-29.9)	260	26 (27.4)	234 (24.3)	1.98 (1.15-3.35)	1.79 (1.04-3.06)
obese (BMI ≥30)	142	34 (35.8)	106 (11.0)	5.68 (3.38-9.55)	5.42 (3.20-9.21)

Abbreviations: BMI, body mass index; CI, confidence interval; HTD, hypertensive disorder of pregnancy; OR, odds ratio.

[a] Adjusted for parity, multiple gestation and maternal age. Cases and controls are matched on year of birth and restricted to women without registered diabetes during pregnancy.

Table 3 - Association of Body Mass Index with Hypertensive Disorders during Pregnancy Stratified by Smoking Status

	Total N	Cases n (%)	Controls n (%)	Adjusted OR[a] (95% CI)	Total N	Cases n (%)	Controls n (%)	Adjusted OR[a] (95% CI)
Any HTD	1124	402 (100)	722 (100)		259	65 (100)	194 (100)	
Normal weight (BMI <24.9)	669	199 (49.5)	470 (65.1)	1	148	26 (40.0)	122 (62.9)	1
Overweight (BMI25-29.9)	289	116 (28.9)	173 (24.0)	1.78 (1.31-2.42)	73	22 (33.8)	51 (26.3)	2.04 (1.05-3.96)
Obese (BMI >30)	166	87 (21.6)	79 (10.9)	2.98 (2.07-4.31)	38	17 (26.2)	21 (10.8)	3.91 (1.78-8.59)
Preeclampsia	975	253	722		242	48	194	
Normal weight (BMI <24.9)	607	137 (54.2)	470 (65.1)	1	141	19 (39.6)	122 (62.9)	1
Overweight (BMI25-29.9)	245	72 (28.5)	173 (24.0)	1.68 (1.18-2.40)	69	18 (37.5)	51 (26.3)	2.29 (1.09-4.79)
Obese (BMI >30)	123	44 (17.3)	79 (10.9)	2.19 (1.41-3.41)	32	11 (22.9)	21 (10.8)	3.41 (1.38-8.45)
Gestational hypertension	789	67	722		200	6	194	
Normal weight (BMI <24.9)	503	33 (49.3)	470 (65.1)	1	124	2 (33.3)	122 (62.9)	1
Overweight (BMI25-29.9)	193	20 (29.9)	173 (24.0)	1.75 (0.96-3.21)	54	3 (50)	51 (26.3)	3.74 (0.58-23.91)
Obese (BMI >30)	93	14 (20.9)	79 (10.9)	2.73 (1.37-5.46)	22	1 (16.7)	21 (10.8)	3.18 (0.26-38.44)
Pre-existing hypertension	804	82	722		205	11	194	
Normal weight (BMI <24.9)	499	29 (35.4)	470 (65.1)	1	127	5 (45.5)	122 (62.9)	1
Overweight (BMI25-29.9)	197	24 (29.2)	173 (24.0)	1.99 (1.11-3.58)	52	1 (9)	51 (26.3)	0.52 (0.06-4.64)
Obese (BMI >30)	108	29 (35.4)	79 (10.9)	5.87 (3.37-10.56)	26	5 (45.5)	21 (10.8)	6.28 (1.62-24.41)

Abbreviations: BMI, body mass index; CI, confidence interval; HTD, hypertensive disorder of pregnancy; OR, odds ratio.

[a] Adjusted for parity, multiple gestation and maternal age. Cases and controls are matched on year of birth and restricted to women without registered diabetes during pregnancy

Table 4 - Association of Body Mass Index with Hypertensive Disorders during Pregnancy Stratified by Preterm Births

	Preterm Pregnancy (<37 weeks)				Full-term Pregnancy (≥ 37 weeks)			
	Total N	Cases n (%)	Controls n (%)	Adjusted OR[a] (95% CI)	Total N	Cases n (%)	Controls n (%)	Adjusted OR[a] (95% CI)
Any HTD	161	90 (100)	71 (100)		1278	390 (100)	888 (100)	
Normal weight (BMI <24.9)	104	56 (62.2)	48 (67.6)	1	746	173 (44.4)	573 (64.5)	1
Overweight (BMI25-29.9)	41	24 (26.7)	17 (23.9)	1.21 (0.56-2.60)	333	117 (30.0)	216 (24.3)	1.98 (1.48-2.66)
Obese (BMI >30)	16	10 (11.1)	6 (8.5)	1.67 (0.54-5.23)	199	100 (25.6)	99 (11.2)	3.78 (2.69-5.33)
Preeclampsia	147	76	71		1122	234	888	
Normal weight (BMI <24.9)	97	49 (64.5)	48 (67.6)	1	683	110 (47.0)	573 (64.5)	1
Overweight (BMI25-29.9)	37	20 (26.3)	17 (23.9)	1.20 (0.54-2.64)	288	72 (30.8)	216 (24.3)	2.04 (1.43-2.91)
Obese (BMI >30)	13	7 (9.2)	6 (8.5)	1.28 (0.38-4.33)	151	52 (22.2)	99 (11.2)	3.19 (2.10-4.83)
Gestational hypertension	74	3	71		960	72	888	
Normal weight (BMI <24.9)	50	2 (66.7)	48 (67.6)	1	606	33 (45.8)	573 (64.5)	1
Overweight (BMI25-29.9)	18	1 (33.3)	17 (23.9)	1.00 (0.08-12.85)	238	22 (30.6)	216 (24.3)	1.84 (1.03-3.28)
Obese (BMI >30)	6	0	6 (8.5)	-	116	17 (23.6)	99 (11.2)	3.08 (1.63-5.83)
Pre-existing hypertension	82	11	71		972	84	888	
Normal weight (BMI <24.9)	53	5 (45.4)	48 (67.6)	1	603	30 (35.7)	573 (64.5)	1
Overweight (BMI25-29.9)	20	3 (27.3)	17 (23.9)	2.07 (0.39-10.98)	239	23 (27.4)	216 (24.3)	1.80 (1.01-3.21)
Obese (BMI >30)	9	3 (27.3)	6 (8.5)	14.37 (1.39-148.6)	130	31 (36.9)	99 (11.2)	5.69 (3.25-9.93)

Abbreviations: BMI, body mass index; CI, confidence interval; HTD, hypertensive disorder of pregnancy; OR, odds ratio.

[a] Adjusted for parity, multiple gestation and maternal age. Cases and controls are matched on year of birth and restricted to women without registered diabetes during pregnancy

Supplementary Table 1 – Characteristics of women with and without body mass index values measured in early pregnancy

	Total n (%)	Missing values n (%)	BMI values n (%)	p-values
Total	1497 (100)	52 (100)	1445 (100)	
Hypertension				
No	996 (67%)	34 (65%)	962 (67%)	0.07
Preexisting	97 (6%)	2 (4%)	95 (7%)	
Gestational	81 (5%)	6 (12%)	75 (5%)	
Preeclampsia	319 (21%)	9 (17%)	310 (21%)	
superimposed	4 (0%)	1 (2%)	3 (0%)	
Age, years				
< 25	419 (28%)	10 (19%)	409 (28%)	0.067
25-34	820 (55%)	27 (52%)	793 (55%)	
≥ 35	258 (17%)	15 (29%)	243 (17%)	
Nationality				
Icelandic	1457 (97%)	47 (90%)	1410 (98%)	0.008
Other	37 (3%)	5 (10%)	32 (2%)	
Missing	3 (0)	0	3 (0%)	
Residency				
capital area	1,122 (75%)	35 (67%)	1,087 (75%)	0.14
non capital area	271 (18%)	14 (27%)	257 (18%)	
Missing	104 (7%)	3 (6%)	101 (7%)	
Cohabitation				
lives with other parent	1283 (86%)	45 (87%)	1238 (95%)	1.0
Single	212 (14%)	7 (13%)	205 (5%)	
Missing	2 (0%)	0	2 (0%)	
Working status				
paid work	1,083 (72%)	37 (71%)	1,046 (72%)	0.43
Homemarker, not working	30 (2%)	2 (4%)	28 (2%)	
Student	202 (13%)	5 (10%)	197 (14%)	
Other	182 (12%)	8 (15%)	174 (12%)	
Parity				
0	676 (45%)	17 (33%)	659 (46%)	0.084
1	452 (30%)	16 (31%)	436 (30%)	
≥ 2	369 (25%)	19 (37%)	350 (24%)	
Multiple gestation				
No	1,395 (93%)	47 (90%)	1,348 (93%)	0.4
Yes	102 (7%)	5 (10%)	97 (7%)	

Abbreviations: BMI, body mass index; p-value, Fisher Exact Test for difference in proportions between BMI availability.

Supplementary Table 2 – Linear regression table with covariates for Figure 1.

Panel A

	SBP during 1st check	DBP during 1st check	SBP during final check	DBP during final check
(intercept)	110.2*** (106.82, 113.48)	63.8*** (61.35, 66.33)	116.0*** (112.65, 119.40)	77.1*** (74.58, 79.65)
Hypertension (No/Yes)	8.0*** (6.66, 9.34)	6.2*** (5.21, 7.21)	18.9*** (17.52, 20.23)	17.0*** (15.93, 17.97)
Parity - 1	0.8 (-0.74, 2.39)	0.7 (-0.50, 1.85)	-0.2 (-1.76, 1.42)	-0.9 (-2.08, 0.31)
Parity - 2	0.4 (-1.44, 2.31)	0.5 (-0.93, 1.88)	-2.3** (-4.17, -0.37)	-1.1 (-2.50, 0.35)
Multiple gestation (No/Yes)	-2.6** (-5.08, -0.12)	-0.6 (-2.47, 1.24)	0.5 (-2.04, 2.99)	2.0** (0.12, 3.89)
Maternal age at birth	0.2*** (0.05, 0.31)	0.2*** (0.11, 0.30)	0.2** (0.03, 0.29)	0.1 (-0.03, 0.16)
Observations	1,426[a]	1,426[a]	1,438[b]	1,438[b]
R^2	0.1	0.11	0.36	0.45
Adjusted R^2	0.09	0.11	0.36	0.45

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

*p<0.1; **p<0.05; ***p<0.01;
[a] 19 missing values;
[b] 7 missing values.

Supplementary Table 2 (cont.) – Linear regression table with covariates for Figure 1.

Panel B

	SBP during 1st check	DBP during 1st check	SBP during final check	DBP during final check
(intercept)	111.7*** (108.45, 115.00)	65.2*** (62.75, 67.63)	115.4*** (111.99, 118.76)	76.8*** (74.27, 79.36)
Pre-existing hypertension (No/Yes)	16.7*** (14.25, 19.16)	13.3*** (11.49, 15.14)	16.8*** (14.22, 19.32)	15.9*** (13.96, 17.80)
Gestational hypertension (No/Yes)	7.6*** (4.85, 10.33)	6.7*** (4.69, 8.77)	15.5*** (12.67, 18.36)	15.6*** (13.48, 17.76)
Preeclampsia (No/Yes)	5.2*** (3.66, 6.73)	3.7*** (2.57, 4.85)	20.4*** (18.80, 21.96)	17.6*** (16.43, 18.81)
Parity - 1	0.4 (-1.10, 1.97)	0.4 (-0.78, 1.50)	-0.1 (-1.66, 1.51)	-0.8 (-2.03, 0.36)
Parity - 2	-0.04 (-1.88, 1.79)	0.1 (-1.26, 1.47)	-2.2** (-4.13, -0.34)	-1.1 (-2.48, 0.37)
Multiple gestation (No/Yes)	-1.9 (-4.29, 0.57)	0.02 (-1.79, 1.83)	0.2 (-2.32, 2.70)	1.9* (-0.02, 3.76)
Maternal age at birth	0.1** (0.01, 0.26)	0.2*** (0.07, 0.25)	0.2*** (0.05, 0.31)	0.1 (-0.02, 0.17)
Observations	1,426[a]	1,426[a]	1,438[b]	1,438[b]
R^2	0.14	0.16	0.37	0.45
Adjusted R^2	0.13	0.16	0.36	0.45

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

*p<0.1; **p<0.05; ***p<0.01;
[a] 19 missing values;
[b] 7 missing values.

Panel A

Panel B

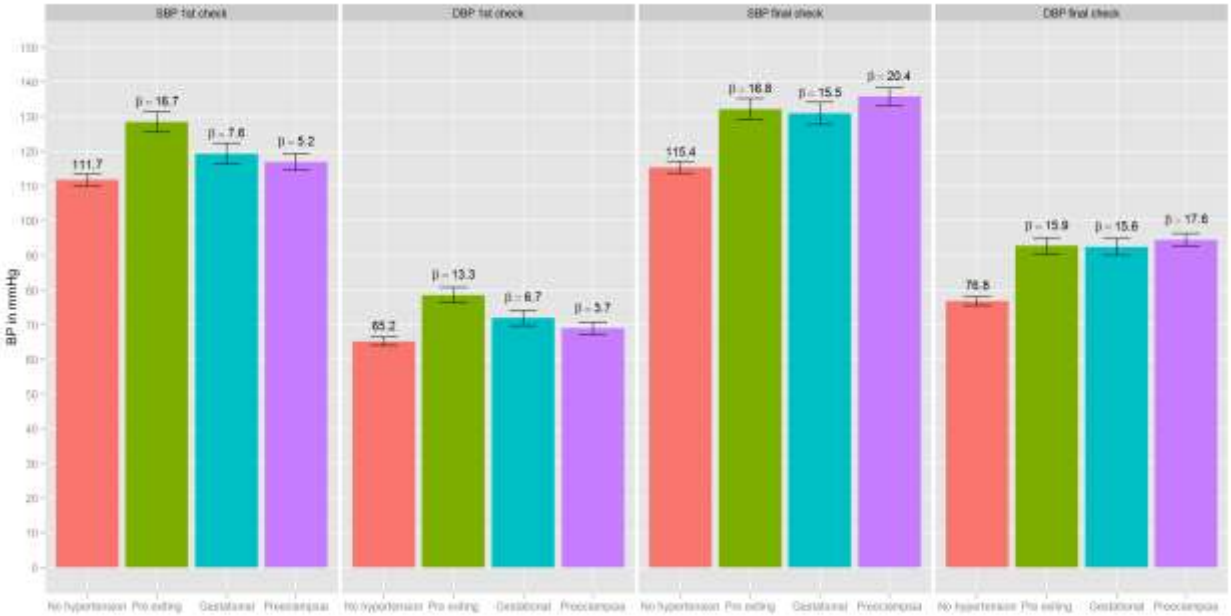

Figure 1 – Women's blood pressure levels (mm Hg) according to diagnosis of hypertensive disorder of pregnancy. *****Mean values of mm Hg are adjusted for parity, multiple gestation and maternal age in with linear regression models. Beta values demonstrate the adjusted the difference of mean mmHg value by diagnosis.