Best Practice & Research Clinical Endocrinology & Metabolism 33 (2019) 127–132

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

11

# Prevention of pre-eclampsia after infertility treatment: Preconceptional minimalisation of risk factors

Hanna Hürter, Consultant, MD [a],
Shane Vontelin van Breda, Postdoc, PhD [c],
Lenka Vokalova, Postdoc, PhD [c],
Marlene Brandl, Resident, MD [a],
Marc Baumann, Consultant, MD [d],
Irene Hösli, Head of Department, MD [a, c],
Evelin Annegret Huhn, Consultant, MD [a, c],
Christian De Geyter, Head of the Department, MD [b, c],
Simona W. Rossi, Principal Investigator, PhD [c],
Olav Lapaire, Deputy Head of Department, MD [a, c, *]

[a] *Department of Obstetrics, University Women's Hospital, University of Basel, Basel, Switzerland*
[b] *Reproductive Medicine and Gynecological Endocrinology (RME), University Hospital, University of Basel, Vogesenstrasse 124, 4031, Basel, Switzerland*
[c] *Department of Biomedicine (DBM), University Hospital, University of Basel, Basel, Switzerland*
[d] *Department of Obstetrics and Gynaecology, University Hospital Bern, Bern, Switzerland*

ARTICLE INFO

*Article history:*
Available online 15 May 2019

*Keywords:*
pre-eclampsia
infertility
obesity
blood pressure
pregnancy
preconception

Although an increased risk of pre-eclampsia in pregnancies conceived after infertility treatment has been reported, it remains unknown whether preconceptional minimalisation of known risk factors would help in preventing pre-eclamsia. Obesity and pre-conceptional blood pressure are discussed as major risks for the development of pre-eclampsia and low doses of aspirins, folic acid, statins and metformin are discussed as potential preventive treatments to decrease the risk of pre-eclampsia. In the present review we discuss whether present-day reproductive medicine could progress towards complication-free pregnancy.



* Corresponding author. Department of Obstetrics, University Women's Hospital, University of Basel, Basel, Switzerland.
*E-mail address:* olav.lapaire@usb.ch (O. Lapaire).

https://doi.org/10.1016/j.beem.2019.05.001
1521-690X/

## Introduction

Pregnancies arising after infertility treatment are often burdened with significantly higher complication rates. Pre-eclampsia, a pregnancy-specific syndrome, affects 2–5% of pregnancies in developed countries. Interestingly, pre-eclampsia is particularly common in women that have undergone infertility treatment. Recent studies have demonstrated that the incidence of pre-eclampsia can be decreased with low dose aspirin when initiated before 16 weeks of gestation. During preconception, many risk factors leading to pre-eclampsia may be identified during infertility work-up. Therefore, can reproductive medicine including preconceptional diagnostic workup be of any assistance in the development towards complication-free pregnancy? Is there a place for preconceptional modification of pre-existing risk factors (see Fig. 1)?

## Pre-eclampsia and obesity: a complex relationship

The prevalence of obesity (BMI $\geq$30 kg/m$^2$) in women of reproductive-age has been increasing worldwide during the last decade. Pre-existent obesity reduces fertility and also increases the risk of obesity-related comorbidities such as arterial hypertension and diabetes mellitus, which subsequently increases the likelihood of adverse maternal and neonatal outcomes if pregnancy occurs. Recent estimates suggest that more than 21% of women worldwide will be obese in 2025 [1]. Obesity increases the risk of pregnancy-induced hypertension and pre-eclampsia by 3–10 times [2], increased by 3–10 times [3,4]. In a meta-analysis, Raham and colleagues reported an increased risk for pre-eclampsia in obese women [OR: 3.87 (3.48–4.29)], compared to overweight women [OR: 1.98 (1.64–2.40)] and underweight pregnant women [OR: 0.70 (0.59–0.83)] [5].

In general, interventions to improve the maternal preconceptional weight are either diet-based, physical-activity-based, or a combination of both approaches. The National Institute for Health and Care Excellence (NICE) in England published its recommendation for a healthy diet together with at least 30 min of physical activity once a day in England [6], or with 150 min per week being advised in the USA [6]. Physical activity should not achieve maximal fitness, but should instead strengthen the physical condition with activities such as brisk walking or swimming.

Furthermore, women with a BMI >35 kg/m$^2$ should receive counselling from a dietitian [National Institute for Health and Care Excellence 2010]. Among lifestyle interventions, those based on a

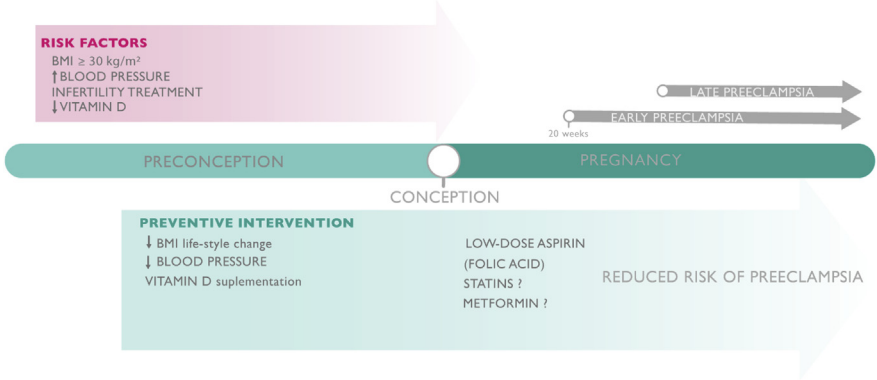


**Fig. 1. Suggestion of intervention to reduce the risk of pre-eclampsia development following infertility treatment**. As preventive intervention to be considered before conception are changes in life style to reduce BMI or reduction of diagnosed high blood pressure. Treatments to be considered after conception to reduce the risk of pre-eclampsia are the administration of low doses of aspirin and eventually administration of folic acid, statins or metformin.

modified diet are the most effective and may have a positive impact on maternal outcome and pre-eclampsia, although studies included in a meta-analysis were small and heterogeneous [7]. Another meta-analysis showed a non-significant increase in the incidence of pre-eclampsia of 0.2% per gained kilogram, (95% confidence interval [CI] 0.5–0.9%, $p > 0.05$) [8]. A significant challenge for intervention studies has been the compliance of the participants, with an inconsistency of up to 25% being noted. The inconsistency especially occurs in cases of physical interventions [9]. Nevertheless, the pre-conceptional period is critical and a perfect moment to begin behavioural changes, leading to a diminished of risk for pre-eclampsia.

## Preconception: a critical period to lower high blood pressure

Arterial hypertension, a leading cause of death among women also increases the risk of pregnancy complications, especially pre-eclampsia [10]. Therefore, an essential component of preconception care consists of interventions involving the reduction of blood pressure, i.e., modification of diet and physical activity. The prevalence of arterial hypertension is high and involves up to 8% of women of reproductive-age [10]. Despite sufficient evidence that a change in diet and an increase in physical activity helps lower blood pressure, few studies have focused on women of reproductive-age [10]. A consumer survey of adults in the USA reported that adults of reproductive-age were less likely to receive advice from their health care provider than those aged over 65 years [11]. The study of Bombard et al. [10] revealed that the majority of women of reproductive-age (63.2% between the ages of 35–44) and with self-reported arterial hypertension received advice from their health care providers. Besides health care advice, a valuable tool for lifestyle modification is preconception clinical visits during which all women receive risk assessments and informed counselling with instructions.

Furthermore, patients may be referred to services providing lifestyle changes. The results from Bombard et al. [10] suggest that advice given to a group of reproductive-aged women lead to a successful change in behaviour. To decrease their blood pressure, most women in the group of reproductive-age with self-reported arterial hypertension modified their diet (75.5%), reduced daily salt intake (80.4%), increased physical activity (70.1%) and reduced alcohol intake (67.8%). Therefore, the implementation of individual counselling and instructions to change lifestyle and improve blood pressure in hypertensive reproductive-aged women during preconceptional care visits is an essential tool to optimise pregnancy outcomes and minimise the risk of pre-eclampsia.

## Low vitamin D levels and the risk of pre-eclampsia

Many observational studies reported a significant association between an increased risk of pre-eclampsia and low Vitamin D levels, although the exact mechanisms are not fully understood [12] pre-eclampsia. A Canadian Meta-Analysis including 31 observational studies found a higher risk of the development of pre-eclampsia in case of low Vitamin D levels (<50 nmol/L) [12]. However, to date the question remains to be answered, whether the supplementation of Vitamin D, alone or in combination with Calcium, is as effective als Calcium alone in case of women with a low Calcium intake [13]. Ideally, Vitamin D levels should be assessed preconceptionally and corrected in case of low levels.

## Preconceptionally initiated low-dose aspirin for the prevention of pre-eclampsia

Low dose aspirin (75–150 mg per day) starting before 16 weeks of gestation is widely used to prevent early-onset pre-eclampsia (before 34 weeks of gestation) with a risk reduction of 0.47 (95% CI 0.34–0.65) [14,15]. Since studies have shown an increased risk for developing pregnancy-induced hypertension (PIH) and pre-eclampsia after reproductive therapy [16,17],low-dose aspirin may be helpful in this group of women. In contrast to a placebo-controlled trial, which showed a lower

incidence of hypertensive disorders after preconceptionally initiated low-dose aspirin [18], a meta-analysis did not support the hypothesis that preconceptionally initiated low-dose aspirin after in vitro fertilization with continuation during the first trimester reduces the risk of hypertensive disorders during pregnancy in singleton [OR 0.62 (95% CI 0.22–1.7)] or twin pregnancies [OR 1.2 (95% CI 0.35–4.4)] [19].

## Can folic acid be helpful for the prevention of pre-eclampsia?

Folic acid supplementation with 0.4–0.5 mg daily is recommended worldwide for the prevention of neural tube defects. Observational data have indicated that folic acid may decrease the risk of pre-eclampsia as well [20].

Furthermore, data from the Ottawa and Kingston (OaK) Birth Cohort indicated a 60% reduction in the risk of pre-eclampsia as well as a dose–response association between folic acid and the risk of pre-eclampsia in high-risk women [21]. However, data from a recently published double-blinded multicentre randomized controlled trial of a high-risk cohort using 4 mg of folic acid versus a placebo between eight and sixteen weeks of gestation showed a similar risk of pre-eclampsia in both groups (relative risk 1.10, 95% confidence interval 0.90 to 1.34; $P = 0.37$) [22].

## Statins

Pre-eclampsia and cardiovascular diseases show similarities as far as their pathophysiology is concerned. According to this, pravastatin has been discussed to be useful in preventing pre-eclampsia. Pilot clinical studies have shown promising data to prove this hypothesis. In various animal studies pravastatin could reduce the rates of pregnancy loss and fetal growth restriction, lower blood pressure, promote the release of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and suppress the production of anti-angiogenic factors, i.e., soluble FMS-like tyrosine kinase (sFlt-1) and soluble endoglin (s-Eng) [23–28]. Similar results were also shown in a small single pilot trial in humans [29]. This is a potentially promising therapy for the prevention of pre-eclampsia in high-risk women [30]. However, more trials of safety and efficacy with larger cohorts are required before considering statin therapy for the prevention of pre-eclampsia [31–33]. However, it has to be mentioned that statins are currently contraindicated during pregnancy, and their use and safety has to be the topic of further studies.

## Metformin

Metformin, as an insulin-sensitising drug, is used for infertility treatment of women affected by polycystic ovary syndrome (PCOS). During pregnancy, the benefit of metformin has not yet been sufficiently demonstrated. However, according to recent published data, metformin is not associated with an increased risk of significant congenital disabilities when used in women with PCOS during the first trimester [34]. In one randomised clinical trial, metformin administration during early pregnancy was shown to reduce the incidence of pre-eclampsia [35]. Still, clinical experience is rare, and drug safety during pregnancy has still to be proven. Further studies are required to investigate the use of metformin in the prevention of pre-eclampsia.

## Conclusion

Despite promising progress in the understanding of the pathophysiology of pre-eclampsia, little advances in preconceptional prevention have been registered so far. The pronounced heterogeneity of this syndrome can partially explain and account for 14% of maternal deaths worldwide that range from the early onset pre-eclampsia with impaired placental implantation up to late-onset pre-eclampsia with dominantly maternal manifestations. Ongoing efforts and bidirectional research between

laboratories and clinics are therefore urgently needed to find additional preventive strategies and to lower the incidence of this disease.

**Practice points**

- Pregnancies arising after infertility treatment are often burdened with significantly higher complication rates, such as pre-eclampsia.
- During preconception, many risk -factors leading to pre-eclampsia may be identified during infertility work-up.
- The preconceptional period is critical and a perfect moment to begin behavioral changes leading to a diminished of risk for pre-eclampsia.
- Despite promising progress in the understanding of the pathophysiology of pre-eclampsia, little advances in preconceptional prevention have been registered so far.

**Research agenda**

- More studies are needed to improve the maternal preconceptional weight and to lower the prevalence of obesity in women of reproductive-age.
- Additional research is needed to assess the effect of changes in diet and an increase in physical activity to lower blood pressure in women of reproductive-age.
- Further studies are required to investigate the use of metformin in the prevention of pre-eclampsia
- Ongoing efforts and bidirectional research between laboratories and clinics are urgently needed to find additional preventive strategies and to lower the incidence of pre-eclampsia.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, ornot-for-profit sectors.

## Declaration of interest

The authors declare no potential competing interest.

## References

[1] NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016;387:1513–30. https://doi.org/10.1016/S0140-6736(16)00618-8.
[2] Kim SS, Zhu Y, Grantz KL, et al. Obstetric and neonatal risks among obese women without chronic disease. Obstet Gynecol 2016;128:104–12. https://doi.org/10.1097/AOG.0000000000001465.
*[3] Wang Z, Wang P, Liu H, et al. Maternal adiposity as an independent risk factor for pre-eclampsia: a meta-analysis of prospective cohort studies. Obes Rev 2013;14:508–21. https://doi.org/10.1111/obr.12025.
[4] Marchi J, Berg M, Dencker A, et al. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obes Rev 2015;16:621–38. https://doi.org/10.1111/obr.12288.
*[5] Rahman MM, Abe SK, Kanda M, et al. Maternal body mass index and risk of birth and maternal health outcomes in low- and middle-income countries: a systematic review and meta-analysis. Obes Rev 2015;16:758–70. https://doi.org/10.1111/obr.12293.
[6] Services H, Health UDO. Pregnancy. Staying healthy and safe. https://www.womenshealth.gov/pregnancy/youre-pregnant-now-what/staying-healthy-and-safe.
[7] Thangaratinam S, Rogozinska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. BMJ 2012;344. https://doi.org/10.1136/bmj.e2088. e2088–8.

*[8] Ruifrok AE, van Poppel MNM, van Wely M, et al. Association between weight gain during pregnancy and pregnancy outcomes after dietary and lifestyle interventions: a meta-analysis. Am J Perinatol 2014;31:353–64. https://doi.org/10.1055/s-0033-1352484.

*[9] Poston L, Briley AL, Barr S, et al. Developing a complex intervention for diet and activity behaviour change in obese pregnant women (the UPBEAT trial); assessment of behavioural change and process evaluation in a pilot randomised controlled trial. BMC Pregnancy Childbirth 2013;13:148. https://doi.org/10.1186/1471-2393-13-148.

[10] Bombard JM, Robbins CL, Dietz PM, et al. Preconception care: the perfect opportunity for health care providers to advise lifestyle changes for hypertensive women. Am J Health Promot 2013;27:S43–9. https://doi.org/10.4278/ajhp.120109-QUAN-6.

[11] Valderrama AL, Tong X, Ayala C, et al. Prevalence of self-reported hypertension, advice received from health care professionals, and actions taken to reduce blood pressure among US adults–HealthStyles, 2008. J Clin Hypertens (Greenwich) 2010;12:784–92. https://doi.org/10.1111/j.1751-7176.2010.00323.x.

*[12] Aghajafari F, Nagulesapillai T, Ronksley PE, et al. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ 2013;346. https://doi.org/10.1136/bmj.f1169. f1169–9.

[13] Hofmeyr GJ, Lawrie TA, Atallah ÁN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2014;3(Suppl. 1):24–132. https://doi.org/10.1002/14651858.CD001059.pub4.

*[14] Bujold E, Roberge S, Lacasse Y, et al. Prevention of pre-eclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstet Gynecol 2010;116:402–14. https://doi.org/10.1097/AOG.0b013e3181e9322a.

[15] Askie LM, Duley L, Henderson-Smart DJ, et al. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. The Lancet 2007;369:1791–8. https://doi.org/10.1016/S0140-6736(07)60712-0.

[16] Shevell T, Malone FD, Vidaver J, et al. Assisted reproductive technology and pregnancy outcome. Obstet Gynecol 2005;106:1039–45. https://doi.org/10.1097/01.AOG.0000183593.24583.7c.

[17] Allen VM, Wilson RD, Cheung A, Genetics Committee, Reproductive Endocrinology and Infertility Committee. Pregnancy outcomes after assisted reproductive technology. J Obstet Gynaecol Can 2006;28:220–33. https://doi.org/10.1016/S1701-2163(16)32112-0.

*[18] Lambers MJ, Groeneveld E, Hoozemans DA, et al. Lower incidence of hypertensive complications during pregnancy in patients treated with low-dose aspirin during in vitro fertilization and early pregnancy. Hum Reprod 2009;24:2447–50. https://doi.org/10.1093/humrep/dep245.

[19] Groeneveld E, Lambers MJ, Lambalk CB, et al. Preconceptional low-dose aspirin for the prevention of hypertensive pregnancy complications and preterm delivery after IVF: a meta-analysis with individual patient data. Hum Reprod 2013;28:1480–8. https://doi.org/10.1093/humrep/det022.

*[20] Bulloch RE, Lovell AL, Jordan VMB, et al. Maternal folic acid supplementation for the prevention of pre-eclampsia: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 2018;32:346–57. https://doi.org/10.1111/ppe.12476.

[21] Walker MC, Finkelstein SA, Rennicks White R, et al. The Ottawa and Kingston (OaK) birth cohort: development and achievements. J Obstet Gynaecol Can 2011;33:1124–33.

[22] Wen SW, White RR, Rybak N, et al. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. BMJ 2018;362:k3478. https://doi.org/10.1136/bmj.k3478.

[23] Cudmore M, Ahmad S, Al-Ani B, et al. Negative regulation of soluble Flt-1 and soluble endoglin release by heme oxygenase-1. Circulation 2007;115:1789–97. https://doi.org/10.1161/CIRCULATIONAHA.106.660134.

[24] Kumasawa K, Ikawa M, Kidoya H, et al. Pravastatin induces placental growth factor (PGF) and ameliorates pre-eclampsia in a mouse model. Proc Natl Acad Sci USA 2011;108:1451–5. https://doi.org/10.1073/pnas.1011293108.

[25] Ahmed A, Singh J, Khan Y, et al. A new mouse model to explore therapies for pre-eclampsia. PLoS One 2010;5:e13663. https://doi.org/10.1371/journal.pone.0013663.

[26] Saad AF, Kechichian T, Yin H, et al. Effects of pravastatin on angiogenic and placental hypoxic imbalance in a mouse model of pre-eclampsia. Reprod Sci 2014;21:138–45. https://doi.org/10.1177/1933719113492207.

[27] Fox KA, Longo M, Tamayo E, et al. Effects of pravastatin on mediators of vascular function in a mouse model of soluble Fms-like tyrosine kinase-1-induced pre-eclampsia. Am J Obstet Gynecol 2011;205:366. https://doi.org/10.1016/j.ajog.2011.06.083. e1–5.

[28] Singh J, Ahmed A, Girardi G. Role of complement component C1q in the onset of pre-eclampsia in mice. Hypertension 2011;58:716–24. https://doi.org/10.1161/HYPERTENSIONAHA.111.175919.

[29] Costantine MM, Tamayo E, Lu F, et al. Using pravastatin to improve the vascular reactivity in a mouse model of soluble fms-like tyrosine kinase-1-induced pre-eclampsia. Obstet Gynecol 2010;116:114–20. https://doi.org/10.1097/AOG.0b013e3181e10ebd.

*[30] Katsi V, Georgountzos G, Kallistratos MS, et al. The role of statins in prevention of pre-eclampsia: a promise for the future? Front Pharmacol 2017;8:247. https://doi.org/10.3389/fphar.2017.00247.

[31] McGrogan A, Snowball J, Charlton RA. Statins during pregnancy: a cohort study using the General Practice Research Database to investigate pregnancy loss. Pharmacoepidemiol Drug Saf 2017;26:843–52. https://doi.org/10.1002/pds.4176.

[32] Godfrey LM, Erramouspe J, Cleveland KW. Teratogenic risk of statins in pregnancy. Ann Pharmacother 2012;46:1419–24. https://doi.org/10.1345/aph.1R202.

[33] Kusters DM, Hassani Lahsinoui H, van de Post JAM, et al. Statin use during pregnancy: a systematic review and meta-analysis. Expert Rev Cardiovasc Ther 2012;10:363–78. https://doi.org/10.1586/erc.11.196.

[34] Cassina M, Donà M, Di Gianantonio E, et al. First-trimester exposure to metformin and risk of birth defects: a systematic review and meta-analysis. Hum Reprod Update 2014;20:656–69. https://doi.org/10.1093/humupd/dmu022.

*[35] Brownfoot FC, Hastie R, Hannan NJ, et al. Metformin as a prevention and treatment for pre-eclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. Am J Obstet Gynecol 2016;214:356.e1–356.e15. https://doi.org/10.1016/j.ajog.2015.12.019.