Impact of Exercise Training on Preeclampsia
Potential Preventive Mechanisms

Dominique S. Genest, Stéphanie Falcao, Jolanta Gutkowska, Julie L. Lavoie

Abstract—Preeclampsia is characterized by hypertension and de novo proteinuria after 20 weeks of pregnancy. It is the leading cause of perinatal morbidity and mortality in the developed world, and to date, the only means of treating the disease is by inducing delivery. Many studies have shown the benefits of exercise training on normal pregnancy. Conversely, because the impact of exercise on reducing the risk of preeclampsia has long been debated, the American College of Obstetricians and Gynecologists has yet to support the prescription of exercise training to women at risk of developing the disease. There is, however, a significant body of evidence in support of the protective role of exercise training against preeclampsia. A recent animal study demonstrated that many preeclampsia features can be eliminated with prenatal followed by gestational exercise training. Hence, the present article reviews the literature on the impact of exercise training on preeclampsia risk, as well as the mechanisms that may be involved. (Hypertension. 2012;60:1104-1109.) • Online Data Supplement

Key Words: basic science ■ clinical science ■ exercise ■ experimental models ■ preeclampsia/pregnancy ■ inflammation ■ oxidative stress

The benefits of exercise training (ExT) have been widely studied in healthy individuals, as well as in patients with cardiovascular diseases (CVD), such as hypertension and atherosclerosis.1 In addition, it has been shown to improve normal pregnancy outcomes.2 Preeclampsia, a gestational disease, complicates ≈5% to 10% of pregnancies and is the leading cause of maternal and fetal mortality/morbidity in developed countries.3 Given that, to date, the only treatment for this disease is fetal delivery, a simple intervention, such as ExT, may have a profound impact as an adjunctive and prophylactic treatment, if proven to be effective. Although many studies have investigated the potential beneficial impact of ExT on preeclampsia risk, there is still no clear consensus on its effectiveness. This article therefore reviews the literature on this subject and elaborates on the potential mechanisms involved.

Methods
A computer-based review was performed as described in the Methods section in the online-only Data Supplement.

Preeclampsia
The incidence of preeclampsia has risen in the past 20 years4 and will likely keep climbing as a result of the growing obesity pandemic5 and the increased incidence of hypertension and diabetes mellitus.6,7 Moreover, studies suggest that women who experience preeclampsia are more likely to develop cardiovascular diseases later in life.8 Although the development of the disease begins early in pregnancy, clinically, preeclampsia can only be diagnosed after 20 weeks of gestation with the onset of hypertension and proteinuria.9 Other manifestations of the disease include placental alterations, cerebral ischemia, liver abnormalities, cardiac hypertrophy, and impaired vascular reactivity; however, these features are not seen consistently in all women.10 In addition, severe cases of preeclampsia are associated with pulmonary edema, hemolysis, elevated liver enzymes and low platelets syndrome, severe central nervous system symptoms, renal failure, and intrauterine growth restriction.11

In the last decade, there has been an explosion of research on preeclampsia. Nonetheless, it remains a disease of theories, because a number of factors are proposed to be involved, but none have been clearly established to date. For instance, placental abnormalities, oxidative stress, endothelial dysfunction, inflammation, and immunity have all been suggested as being involved in disease progression.12 Epidemiological studies have been useful in shedding light on preeclampsia risk factors, such as type 2 diabetes mellitus, obesity, hypertension, and thrombophilia.3

Consequently, our limited understanding of the pathophysiology creates obstacles for those trying to treat patients affected by preeclampsia. A great deal of research has focused on identifying strategies to treat the disease. Preventive therapies, including the administration of antioxidants, calcium supplements, and antplatelets, have been investigated without much success.12-14 Given this, physicians must strive to control the progression of the disease to prolong gestation. Antihypertensive therapies are critical, because hypertension

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is known to have negative effects on other tissues, such as the heart, kidneys, and brain.\textsuperscript{15} The antihypertensive treatments available to preeclampsia include, methyldopa (an \(\alpha\)-adrenergic agonist), labetalol (an \(\alpha\)- and \(\beta\)-blocker), and nifedipine (a calcium channel antagonist), are considered relatively safe during pregnancy,\textsuperscript{16} although one study did find an association between labetalol and intrauterine growth restriction.\textsuperscript{17} More specifically, methyldopa has been shown to prevent the progression of moderate-to-severe preeclampsia.\textsuperscript{18} Conversely, some antihypertensive drugs are contraindicated because of their teratogenicity, such as inhibitors of the renin-angiotensin system, or physiologically unsuitable mechanism of action, such as diuretics, because of the hypovolemic state associated with preeclampsia.\textsuperscript{16} Although these agents have the potential to control the progression of disease, they are not always effective. In addition, when antihypertensive therapies can no longer control blood pressure, delivery is required to limit negative pregnancy outcomes.

**Impact of ExT on Preeclampsia**

ExT has been shown to lower blood pressure and improve cardiac function in both healthy and hypertensive men and women.\textsuperscript{19} In addition, it improves insulin sensitivity and reduces circulating levels of triglycerides and low-density lipoproteins.\textsuperscript{20} As such, ExT reduces the risks of cardiovascular diseases and type 2 diabetes mellitus\textsuperscript{21} and may improve pregnancy outcomes in patients at risk for preeclampsia by reducing the prevalence of these associated diseases. In addition, the incidence of gestational diseases is greatly increased in obese women\textsuperscript{22} and ExT is well-known to promote weight loss by reducing fat stores and stimulating muscle mass development.\textsuperscript{20} Nonetheless, whereas ExT may play a role via its effect on other medical conditions (Figure), it is also proposed to directly alleviate preeclampsia features.

Epidemiological and clinical studies have shown that ExT may reduce the risk of several gestational diseases, such as gestational diabetes mellitus,\textsuperscript{23} gestational hypertension,\textsuperscript{24} and preeclampsia\textsuperscript{24–33} (see Table S1 in the online-only Data Supplement). More specifically, most studies investigating the impact of physical activity in early pregnancy have demonstrated a significant decrease in preeclampsia risk compared with sedentary women.\textsuperscript{24–26,28} Conversely, some studies have shown no protective role\textsuperscript{33,34} or a nonsignificant decreased risk\textsuperscript{32} with physical activity in pregnancy, although this may be attributable to the small number of cases\textsuperscript{32} or the short evaluation period\textsuperscript{33,34} in these studies. Indeed, the latter\textsuperscript{33} evaluated physical activity in pregnancy based on an assessment of the week before the first prenatal visit. However, studies that found a significant effect of training investigated all pregnancy weeks before this point. Curiously, 2 studies actually demonstrated a nonsignificant deleterious effect on preeclampsia risk either in the highest level of activity group\textsuperscript{35,36} or in women who initiated physical activity during pregnancy\textsuperscript{33} (see Table S2 in the online-only Data Supplement). However, unlike most of the other studies, they included severe cases of preeclampsia, as well as chronic hypertensive patients. Hence, it is possible that excluding these patients may mask this deleterious effect. Therefore, caution should be exerted regarding the intensity and frequency of exercise when it is initiated at the beginning of pregnancy, although additional studies will be required to further investigate this issue.

Regarding the impact of physical activity only before gestation, most studies have found either a significant\textsuperscript{25,27,33} or a nonsignificant\textsuperscript{31,33} decrease in preeclampsia risk. Of those who found a nonsignificant effect, the study by Tyldum et al\textsuperscript{31} evaluated physical activity on average 3.2 years before pregnancy (\(\leq 20\) years before) and, as such, the women’s activity profile may have been different in the year immediately before gestation. In addition, their sedentary group included women who exercised less than once a week and as such were not completely inactive. Put together, these factors may have reduced the detectable effect of physical activity on pregnancy outcome. Moreover, 2 additional studies found no impact of physical activity before pregnancy on preeclampsia risk\textsuperscript{26,32} but both of these included a very small number of cases (<50) and may not have had the statistical power to demonstrate this association. Finally, very few studies\textsuperscript{25,26,32,33} have investigated the effect of exercising both before and during pregnancy, but to date, there is little data to support the hypothesis that the effects are additive.

The first animal study to clearly demonstrate the benefits of ExT in the prevention of preeclampsia-like features has recently been published by our laboratory.\textsuperscript{12} This lends support
to the many, albeit inconclusive, epidemiological findings present to date. Our study was carried out in a mouse model, where female mice overexpressing human angiotensinogen become spontaneously preeclamptic when mated with males overexpressing human renin. The use of animal models enables us to investigate the cause and effect relation between ExT and preeclampsia features, which is impossible to do in women given the many confounding factors present, such as environment and genetics. Sedentary human angiotensinogen mice had many hallmark features of the pathology because they presented with hypertension and proteinuria, as well as cardiac hypertrophy, placental alterations, and impaired vascular reactivity during pregnancy. In addition, placental alterations were associated with an increase in placental vascular endothelial growth factor (VEGF), which may be in response to the hypoxic state of the placenta or to counterbalance the increase in soluble fms-like tyrosine kinase-1 (sFlt-1), an antiangiogenic factor that is often increased in preeclampsia. This may seem to be contradictory to what has been published in the literature, where circulating proangiogenic factors, such as VEGF and the placental growth factor (PIGF), have been typically found to be decreased with preeclampsia. However, these reported decreases correspond to the free form of these factors and may result from the increased concentration of circulating sFlt-1, which binds to these angiogenic factors rather than a decrease in their production. Conversely, ExT before and during gestation prevented most of these preeclampsia-like features. Moreover, placental VEGF was normalized by ExT, although circulating angiogenic markers were not evaluated in our study. Indeed, Weissgerber et al demonstrated a decrease in free PIGF and an increase in antiangiogenic factors, such as sFlt-1, in sedentary pregnant women compared with active women. However, as explained previously, we cannot rule out the possibility that total PIGF levels may have been higher, because it is known to bind to sFlt-1.

**Potential Mechanisms Involved in the Beneficial Impact of Exercise on Preeclampsia**

Little is known concerning the mechanisms by which ExT may reduce the risk of preeclampsia. It has been proposed, however, to promote placental growth and vascular development, reduce oxidative stress, and improve endothelial function, as well as immune and inflammatory responses (Figure).

**Placental Development**

Normal pregnancy necessitates proper invasion of trophoblasts into the uterine artery and myometrial spiral arteries, a step that is often defective in preeclampsia. It has been postulated that the stimulus for normal placental growth may be the periodic reductions in placental perfusion. Indeed, the proliferation of cytotrophoblasts is made possible by the low-oxygen environment present during early pregnancy. Upon invading maternal vessels, the cytotrophoblasts become exposed to higher oxygen levels, which inhibits proliferation and promotes differentiation. This results in the acquisition of an endothelial-like adhesion molecule phenotype of these cells. The low-oxygen environment may also produce placental hypoxia, which stimulates the hypoxia inducible factor-1. This in turn activates VEGF and, in doing so, promotes angiogenesis. Consequently, maternal exercise is beneficial for placental and fetal growth because it diverts blood toward muscle and skin and thus creates a short-lived hypoxic environment. Indeed, trophoblastic, endothelial, and stromal cell proliferation has been shown to be enhanced in placentas from active women during normal pregnancy versus their sedentary counterparts (proliferation index: 45±14 mitoses per 1000 nuclei versus 29±10 mitoses per 1000 nuclei; P<0.008) (Figure). Moreover, placentas from trained mothers have a reduced functional tissue volume (28±4 versus 45±6 cm; P=0.04) and an increased functional volume (434±19 versus 367±14 cm; P=0.006) (Figure). Therefore, the placenta has an improved surface area available for gas and nutrient exchange. As a result, trained women have been reported to have a greater total placental (462±18 versus 414±14 cm²; P=0.05) and fetal (3.75±0.08 versus 3.49±0.07 kg; P=0.05) mass during normal pregnancy, along with a greater placental growth rate (26±2 versus 21±1 cm/week; P=0.04). It is expected that these factors may contribute to reducing fetal complications associated with preeclampsia, such as intrauterine growth restriction.

This is in contrast to earlier studies that reported decreased fetal weight with ExT, likely a result of inadequate maternal caloric intake. Thus, with adequate nutritional intake, fetal development is not hindered but rather improved by ExT.

In addition, improved placentation may reduce the secretion of different mediators that are involved in preeclampsia development. For instance, endothelial dysfunction has been shown to be induced in vitro by combining endothelial cells with serum from preeclamptic women (Figure), supporting the premise that circulating mediators are implicated in the disease. Angiogenic factors have been proposed to be such mediators. Indeed, placental levels of VEGF and PIGF are initially high in normal pregnancy, whereas the level of sFlt-1 is low, which produces a proangiogenic environment. As placental development reaches completion, circulating levels of VEGF and PIGF begin to decline, whereas the level of sFlt-1 rises gradually until the end of pregnancy. Conversely, preeclampsia is characterized by an angiogenic shift, because circulating levels of soluble endoglin (sEng) and sFlt-1, both antiangiogenic factors, are elevated early in pregnancy and progressively more throughout gestation. Both sFlt-1 and sEng inhibit normal placental development by antagonizing circulating VEGF and PIGF, as well as transforming growth factor-β, respectively. It has been proposed that sEng may modulate trophoblastic invasion by affecting the ability of growth factor-β-3 to mediate trophoblastic differentiation. In addition, sEng inhibits endothelial tube formation in vitro, which may be playing a role in causing abnormal placentation.

Interestingly, ExT has been reported to increase circulating PIGF (median [interquartile range]: 278 [221-647] versus 268 pg/mL [159-290 pg/mL]; P=0.014) and reduce circulating sFlt-1 (4217 [2014-5481] versus 5180 pg/mL [4549-5834 pg/mL]; P=0.005) and sEng (7.8 [6.5-10.1] versus 9.1 ng/mL [7.7-16.7 ng/mL]; P=0.025) in late gestation compared with the levels in sedentary pregnant women. This is further supported by data produced by our laboratory in a preeclampsia model, where improved placental development was associated with a normalization of placental VEGF levels in trained...
mice. Hence, ExT may restore angiogenic balance during preeclampsia and improve pregnancy outcome (Figure).

**Oxidative Stress**

Oxidative stress has also been implicated in promoting preeclampsia. The remodeling of uterine and placental vessels generates free radicals, which are normally controlled by appropriate antioxidant levels. In preeclampsia, lipid peroxide levels are elevated, which is associated with a decreased antioxidant defense, such as catalase, glutathione peroxidase, and superoxide dismutase activity.56,57

Interestingly, although acute exercise has been shown to promote oxidative stress, ExT stimulates antioxidant defenses (Figure). For instance, superoxide dismutase and glutathione peroxidase in skeletal muscle, plasma, and liver have been shown to be increased with ExT.58,59 Aerobic conditioning also increases the number of mitochondria in muscles and thus may enable the body to become more resistant to oxidative stress. Indeed, each mitochondrion has a reduced oxidative load, and, as such, more electrons are channeled to cytochrome oxidase rather than producing reactive oxygen species (Figure).60 In addition, exercise diminishes iron’s oxidative capabilities by increasing iron’s binding capacity to apotransferrin61 (Figure). This reduces the circulating ferrous iron61 that catalyzes the Fenton reaction that would otherwise generate reactive oxygen species (Figure). Moreover, lipid peroxidation, a marker of oxidative stress, in the circulation is reduced with ExT,62 providing further support that the body has an improved reactive oxygen species scavenging ability. Hence, by decreasing oxidative stress, ExT may reduce the risk of developing preeclampsia (Figure).

**Endothelial Function**

Endothelial dysfunction is a classic preeclampsia hallmark. For instance, it is thought that the placenta releases the tumor necrosis factor-α into the circulation and, as a result, damages the endothelium by reducing acetylcholine-induced vasodilatation and promoting the production of endothelin.63,64 ExT can, however, reverse this damage by reducing the formation of proinflammatory cytokines and reactive oxygen species, as noted above (Figure). For example, ExT has been shown to reduce the concentration of proinflammatory tumor necrosis factor-α in skeletal muscles65 and in the circulation.66 As a result, this causes a reduction in the levels of endothelin, and, as such, vasoconstriction is diminished. Enhanced shear stress is likely to be another means by which endothelial dysfunction is reversed by ExT.67 This in turn induces endothelial cell proliferation and promotes the expression of endothelial nitric oxide (NO) synthase and antioxidants.68-70 As a result, the increase in endothelial NO synthase leads to enhanced NO production,71 whereas improved antioxidant capacity reduces NO scavenging. This increased NO bioavailability thus enhances vasodilatory responses and contributes to improved endothelial function (Figure). The improved endothelium function observed after ExT could contribute to the blood pressure reduction observed with training72 and may thus contribute to the prevention of preeclampsia.

**Immunity and Inflammation**

During normal pregnancy, there is a diminished innate immune response to prevent fetal rejection with a shift away from cell-mediated immunity toward humoral immunity73 that modifies the expression pattern of proinflammatory cytokines. This equilibrium normally shifts back toward cell-mediated immunity toward the end of pregnancy. In preeclampsia, immunological responses against the fetus are proposed to have a causative pathophysiological role,74 leading to a cell-mediated dominant immunity that adversely affects the coagulation cascade and endothelial function.74 Levels of interferon-γ and proinflammatory factors, such as tumor necrosis factor-α and interleukins (ILs), have been shown to be increased in preeclampsia.75 Proinflammatory cytokines enhance the activity of neutrophils and monocytes, which in turn mediate an inflammatory response and promote endothelial cell damage. For instance, certain cytokines, such as IL-6, impair endothelium-dependent relaxation, thereby contributing to the preeclampsia-associated vasoconstriction.75 Furthermore, elevated levels of thromboxane, in conjunction with decreased prostacyclin, promote endothelial dysfunction and platelet aggregation in already damaged vessels and thus further contribute to the development of hypertension.76

Conversely, although acute exercise may evoke an inflammatory response, regular aerobic exercise has been shown to have anti-inflammatory effects (Figure).42 For instance, in heart-failure patients, ExT reduces circulating levels of proinflammatory mediators, such as IL-1β, IL-6, and tumor necrosis factor-α, whereas it increases circulating anti-inflammatory cytokines, such as IL-10. Platelet-related inflammatory mediators, like P-selectin and soluble CD40 ligand, are also reduced.77 In addition, inflammation-related endothelial damage can be reversed by ExT in patients with cardiovascular diseases. This is characterized by a reduction in peripheral inflammatory markers of endothelial dysfunction, such as granulocyte macrophage colony-stimulating factor, monocyte chemotactic protein-1, soluble intercellular adhesion molecule-1, and soluble vascular cell adhesion molecule-1 (P<0.01).78 Furthermore, components of innate immunity, such as the Toll-like receptor-4, are decreased with ExT (Figure).69 Although the role of Toll-like receptors is not well understood, preeclampsia models have been discovered by infusing low doses of endotoxin, thereby stimulating Toll-like receptor-4.79 As such, this ExT decrease in Toll-like receptor-4 may contribute to promoting an adequate immune response during pregnancy. Put together, these data support the premise that ExT may promote a healthy immune response during pregnancy and, as such, may decrease the risk of preeclampsia by doing so.

Thus, as discussed in this section, ExT improves several pathways that have been implicated in the development of preeclampsia. Therefore, given the heterogeneity in the pathogenesis of preeclampsia, ExT may provide protection to a large population of women affected by this disease (Figure).

**Perspectives**

To date, ExT during pregnancy is not recommended by the American College of Obstetricians and Gynecologists for women at risk of certain gestational complications, such as gestational hypertension and preeclampsia.80 based on studies showing that ExT has deleterious effects on uteroplacental perfusion in at-risk pregnancies.81 Although several studies, as described above, have observed a beneficial effect of ExT
on preeclampsia risk.24–29,33 Overall these are considered insufficient because they are not randomized studies and the mechanisms involved in these effects are unknown.34 Future observational studies will need to investigate not only the impact of exercise, per se, but also aerobic fitness to acquire a better understanding of the role of ExT in preeclampsia prevention. Indeed, a link has been observed between aerobic fitness and hypertension prevention.35 Conversely, the animal study conducted in our laboratory provides evidence that ExT, both before and during gestation, can alleviate preeclampsia-associated features.37 However, more animal studies are required to corroborate these results, in addition to evaluating the impact of ExT when initiated during gestation and at different exercise intensities.

Furthermore, animal models of the disease will be useful because more invasive studies will be essential to determine the specific pathways and tissues involved. Moreover, the type of ExT that seems to be beneficial to women at risk of preeclampsia requires further investigation. Indeed, determining which type of exercise, be it walking or low-impact aerobic training, provides the greatest benefit is necessary, because they produce different adaptations. Hence, much still remains to be done in this field to determine the best course of action in the prescription of ExT to women at risk of preeclampsia.

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**Disclosure**

None.

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Methods

A computer-based review was performed using PubMed, along with the Clinical Trial and WHO clinical databases of all literature published in English and French. No time constraints were imposed regarding publication date. A combination of the following words was used to obtain articles on the effects of exercise on preeclampsia risk: preeclampsia or pre-eclampsia and exercise, exercise training or physical activity. All articles investigating the effects of aerobic conditioning on preeclampsia risk were included in this review, while those evaluating work-related physical activity only were excluded. Indeed, these are often biased by the stress associated with these types of employment. A combination of the following words was used to obtain articles concerning the mechanistic effects of exercise training on preeclampsia prevention: exercise, exercise training or physical activity and immunity, immune, inflammation, angiogenic, pseudovasculogenesis, trophoblastic invasion, preeclampsia, pre-eclampsia, pregnancy, endothelial function, endothelial dysfunction, placenta, oxidative stress, antioxidants, or coagulation.

References


Table S1: Protective role of physical activity on preeclampsia risk

<table>
<thead>
<tr>
<th>First author, year, Study design</th>
<th>Cohort details</th>
<th>Size of study population</th>
<th>Activity details</th>
<th>Main findings</th>
<th>Study limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcoux 1989(1)</td>
<td>Exclusion: HTN (except if due to oral contraceptives)</td>
<td>PE: 172 Ctrl: 505</td>
<td>First 20 weeks of pregnancy</td>
<td>Lower PE risk with greatest energy expenditure (43%) and time (40%). Inverse correlation with time/energy expenditure and PE risk.</td>
<td>Lack of information concerning pre-pregnancy exercise.</td>
</tr>
<tr>
<td>Sorensen 2003(2)</td>
<td>Exclusion: HELLP syndrome, eclampsia, HTN</td>
<td>PE: 201 Ctrl: 383</td>
<td>Pre-pregnancy (12 months) and first 20 weeks of pregnancy</td>
<td>Lower (34%) risk with any physical activity during first 20 weeks. Inverse correlation between time/week or energy expenditure and risk. 33% risk reduction with exercise prior to pregnancy. Lower (41%) risk when exercising before and during pregnancy.</td>
<td>Analysis of the additional benefit of exercising both before and during gestation was limited by the sample size of the subgroups. Inclusion of multiparous women.</td>
</tr>
<tr>
<td>Saftlas 2004(3)</td>
<td>Exclusion: Insulin-dependent diabetes, HTN</td>
<td>PE: 44 Ctrl: 2422</td>
<td>Pre-pregnancy (12 months) and early pregnancy activity (&lt;16 weeks)</td>
<td>Any physical activity at work or in LPTA during pregnancy reduces PE risks. No additional effect of pre-pregnancy LPTA on PE risk.</td>
<td>Small number of cases which compromises evaluation of pre-pregnancy activity (only 14 cases did not exercise).</td>
</tr>
</tbody>
</table>
90mmHg, and proteinuria ≥ 0.3g/day or 2 dipstick ≥ 2+ or 1 catheter sample of 2+.

<table>
<thead>
<tr>
<th>Rudra 2005(4)</th>
<th>Exclusion: HTN, diabetes</th>
<th>PE: 244 Ctrl: 470</th>
<th>Pre-pregnancy exercise (12 months)</th>
<th>Lower PE risk in moderate group (46%) and strenuous/maximal group (78%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective study</td>
<td>Inclusion: nulliparous and multiparous</td>
<td>LTPA perceived exertion: - “moderate” (3 or 4 on Borg scale) - strenuous/maximal” (5 or 6/7-10) Type, frequency and duration</td>
<td>-Inverse relation between PE risk and energy expenditure</td>
<td>No evaluation of gestation physical activity.</td>
</tr>
<tr>
<td>Diagnosis: ACOG* guidelines</td>
<td></td>
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</tbody>
</table>

| Magnus 2008(5) | Inclusion: Singleton births, mild and severe PE, HELLP syndrome, eclampsia | PE: 2315 Ctrl: 57258 | Before 14 and 22 weeks of pregnancy | Lower risk (20%) with frequent activity |
| Prospective study | Diagnosis: Society for Gynecology (Norway) guidelines† | LPTA: frequency | | Intensity and duration were not assessed. Lack of information concerning pre-pregnancy exercise. |

| Rudra 2008(6) | Inclusion: Prenatal care prior to 16 weeks of gestation, ≥18 years, pre-pregnancy | PE: 111 Ctrl: 2130 | Pre-pregnancy (12 months) and a week between 8 and 20 weeks of pregnancy | - Lower PE risk (50%) with moderate intensity only when performed before pregnancy. |
| Prospective study | | | | Assessment of gestational activity was over a short period and may not have been truly representative of |
hypertension and diabetes

**Diagnosis:**
ACOG* guidelines

LPTA: duration, perceived exertion (pre-pregnancy only) and energy expenditure

pregnancy associated with non-significant increase in PE risk.

gestational fitness. N for this analysis was quite small (9 cases)

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**Yeo 2008(7)**

**Exclusion:** HTN, diabetes

**Inclusion:** Previous PE diagnosis, low fitness levels, sedentary lifestyle.

**Diagnosis:** ACOG* guidelines

Stretchers: 38
Walkers: 41

Initiated at 18 weeks of gestation

Tended to be a greater risk reduction in stretching group compared to walkers (incidence of preeclampsia: 2.6% vs. 14.6%, respectively).

No sedentary group, therefore cannot assess the effect of exercise per se.

Group sample size insufficient to demonstrate a significant difference.

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**Hegaard 2010(8)**

**Inclusions:** ≥18 years of age, singleton births, gestational age < 22 weeks

**Diagnosis:** BP ≥ 140/90 mmHg and proteinuria (≥+2) dipstick or 0.3g/24 h

PE: 112
Ctrl: 2681

Pre-pregnancy (12 months)

LTPA categorized as sedentary, light, moderate-to-heavy

Non-significant lower risk with highest degree of physical activity, especially in overweight women

Did not assess gestational physical activity.

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**Tyldum 2010(9)**

**Inclusions:** ≥20 years, singleton births, gestational age ≥ 22 weeks or birth weight above 500g.

**Diagnosis:** SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg

PE: 167
Ctrl: 3489

Pre-pregnancy

Physical activity: frequency, intensity and duration

Non-significant lower PE risk at 120min/week

Information was gathered between 9 months to 20 years before pregnancy (median 3.2 years).

No information concerning pregnancy exercise.

Control group “never/less than once a week”: not
and proteinuria ≥ 1+ on a dipstick

| Fortner 2011(10) | Exclusions: HTN, kidney disease, type II diabetes. | PE: 30 | Pre-pregnancy (12 months) and early pregnancy | - No association between pre-pregnancy total activity and PE risk | Small number of cases |
| Exclusions: HTN, kidney disease, type II diabetes. | Inclusions: Hispanics, age: 16-40yrs, singleton births | Ctrl: 993 | LPTA: frequency, duration and intensity | - Non-significant lower PE risk with total activity during early pregnancy | |
| Diagnosis: BP ≥ 140/90 mmHg, with proteinuria |

Pre-pregnancy total activity and PE risk

Diagnosis in all studies was made after 20 weeks of pregnancy. *ACOG guidelines: 2 BP measurements ≥140/90 mmHg or higher taken 6h apart or a rise of 30 mmHg systolic or 15 mmHg diastolic BP above first trimester values AND proteinuria ≥ 0.3g/day on two or more random specimens collected at least 4 h apart.
† Society for Gynecology guidelines: BP ≥140/90 mmHg after 20 weeks of gestation and proteinuria ≥1 dipstick on at least 2 occasions. PE, preeclampsia; Ctrl, control; LTPA, leisure time physical activity; HTN, hypertension; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.
### Table S2: No protective role or negative effects of physical activity on preeclampsia risk

<table>
<thead>
<tr>
<th>First author, year, Study design</th>
<th>Cohort details</th>
<th>Size of study population</th>
<th>Activity details</th>
<th>Main findings</th>
<th>Study limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osterdal 2009 (11)</strong> Prospective study</td>
<td><strong>Inclusions:</strong> Severe PE, HELLP syndrome, eclampsia. <strong>Diagnosis:</strong> Danish National Patient Registry</td>
<td>PE: 2264 Ctrl: 82875</td>
<td>During the first trimester</td>
<td>No protective effect of LTPA.</td>
<td>No information concerning pre-pregnancy exercise.</td>
</tr>
<tr>
<td><strong>Vollebregt 2010 (12)</strong> Prospective study</td>
<td><strong>Inclusions:</strong> Nulliparous, singleton pregnancy, delivery ≥ 24 wks, HTN <strong>Diagnosis:</strong> DBP≥90 mmHg and proteinuria ≥ 0.3g/24h or dipstick &gt;+2 <strong>Superimposed PE diagnosis:</strong> de novo proteinuria</td>
<td>PE: 128 Ctrl: 3393</td>
<td>Week prior to 1st prenatal care visit</td>
<td>No association between any LTPA (time/week) and PE risk.</td>
<td>No information concerning pre-pregnancy exercise.</td>
</tr>
</tbody>
</table>

Diagnosis in all studies was made after 20 weeks of pregnancy.

PE, preeclampsia; Ctrl, control; LTPA, leisure time physical activity; HTN, hypertension; DBP, diastolic blood pressure.