# Spontaneous Preterm Birth: Is Prevention with Aspirin Possible?

## Die spontane Frühgeburt: Ist eine Prävention mit Aspirin möglich?

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## ABSTRACT

**Background** The rate of preterm births in Germany is 8.6%, which is very high compared to other European countries. As preterm birth contributes significantly to perinatal morbidity and mortality rates, the existing prevention strategies need to be optimized and expanded further. About ⅔ of all women with preterm birth have preterm labor or premature rupture of membranes. They are bracketed together under the term "spontaneous preterm birth" as opposed to iatrogenic preterm birth, for example as a consequence of preeclampsia or fetal growth retardation. Recent studies suggest that low-dose aspirin does not just reduce the rate of iatrogenic preterm births but can also further reduce the rate of spontaneous preterm births. This review article presents the current state of knowledge.

**Method** A selective literature search up until April 2020 was done in PubMed, using the terms "randomized trial", "randomized study", "spontaneous preterm birth", and "aspirin".

**Results** Secondary analyses of prospective randomized studies on the prevention of preeclampsia with low-dose aspirin show that this intervention also significantly reduced the rate of spontaneous preterm births in both high-risk and low-risk patient populations. The results of the ASPIRIN trial, a prospective, randomized, double-blinded multicenter study carried out in six developing countries, also point in this direction, with the figures showing that the daily administration of 81 mg aspirin starting before 14 weeks of gestation lowered the preterm birth rate of nulliparous women without prior medical conditions by around 11% (11.6 vs. 13.1%; RR 0.89; 95% CI: 0.81–0.98, p = 0.012).

**Conclusion** Further studies on this issue are urgently needed. If these confirm the currently available results, then it would be worth discussing whether general aspirin prophylaxis for all pregnant women starting at the latest in 12 weeks of gestation is indicated.

## ZUSAMMENFASSUNG

**Hintergrund** Die Frühgeburtenrate in Deutschland ist mit 8,6% im Vergleich zu anderen europäischen Ländern sehr hoch. Da die Frühgeburt wesentlich zur perinatalen Morbidität und Mortalität beiträgt, müssen die bestehenden Präventionsstrategien weiter optimiert und ausgebaut werden. Circa ⅔ aller Frauen mit Frühgeburt haben vorzeitige Wehentätigkeit oder einen vorzeitigen Blasensprung. Sie werden unter dem Begriff der sogenannten spontanen Frühgeburt zusammengefasst im Gegensatz zur iatrogenen, beispielsweise infolge einer Präeklampsie oder einer fetalen Wachstumsretardierung. Neuere Untersuchungen lassen vermuten, dass mit

niedrigdosiertem Aspirin nicht nur die Rate an iatrogenen, sondern auch an spontanen Frühgeburten weiter reduziert werden kann. Der gegenwärtige Kenntnisstand wird in der vorliegenden Übersichtsarbeit dargestellt.

**Methode** Es erfolgte eine selektive Literatursuche bis April 2020 in PubMed nach den Stichworten „randomized trial", „randomized study", „spontaneous preterm birth", „aspirin".

**Ergebnisse** Sekundäre Analysen von prospektiv-randomisierten Studien zur Prophylaxe der Präeklampsie mit niedrigdosiertem Aspirin zeigen, dass durch diese Intervention auch die Rate an spontanen Frühgeburten sowohl im Hoch- als auch im Niedrigrisikokollektiv signifikant gesenkt wird. In diese Richtung weist auch der ASPIRIN Trial, eine prospektive, randomisierte, doppelblinde Multicenterstudie in 6 Entwicklungsländern, in der nachgewiesen werden konnte, dass durch die tgl. Gabe von 81 mg Aspirin beginnend vor 14 Schwangerschaftswochen die Frühgeburtenrate bei Erstgebärenden ohne Vorerkrankungen um etwa 11 % gesenkt wird (11,6 vs. 13,1 %; RR 0,89; 95 %-KI 0,81–0,98, p = 0,012).

**Schlussfolgerung** Weitere Studien zu dieser Thematik sind dringend notwendig. Sollten diese die vorliegenden Ergebnisse bestätigen, wäre eine generelle Aspirinprophylaxe für alle Schwangeren spätestens ab 12 SSW zu diskutieren.

## Introduction

Preventing preterm births remains an important challenge in obstetrics, because preterm births contribute significantly to perinatal morbidity and mortality rates [1]. The preterm birth rate in Germany has remained stable at 8.6 % [1]. Around ⅔ of all women with preterm birth have preterm labor or premature rupture of membranes or cervical insufficiency. These births are bracketed together under the term "spontaneous preterm birth" in contrast to iatrogenic preterm birth, for example due to preeclampsia, fetal growth retardation or maternal disease.

The pathophysiological causes of preterm birth are many and various. Ascending infection can lead to preterm labor with rupture of membranes. In such cases, microorganisms are recognized by the Toll-like receptors of innate immune system cells, inducing the release of chemokines, cytokines and prostaglandins [2]. We now also know that absent dilatation of the uterine spiral arteries, which has also been discussed as a possible cause of preeclampsia, can lead to preterm labor. It appears that the ensuing uteroplacental ischemia leads to an increased release of prostaglandins, which in their turn induce contractions in the myometrium, triggering destruction of the extracellular matrix in the uterine cervix [2].

As numerous studies have shown, low-dose aspirin can be used to prevent preeclampsia and fetal growth restriction [3, 4]. Aspirin also significantly reduces the preterm rate as was already shown in the CLASP trial and confirmed in later meta-analyses [5 – 7]. Up to now, it was assumed, however, that this primarily affects iatrogenic preterm births.

Whether low-dose aspirin is also able to reduce the rate of spontaneous preterm births is still unknown. Low-dose aspirin blocks the synthesis of thromboxane A2, a vasoconstrictor which also promotes thrombocyte aggregation. It is therefore conceivable that aspirin could counteract uteroplacental ischemia, thereby reducing the associated release of prostaglandins and preventing possible spontaneous preterm birth [8].

A secondary analysis of the "Effects of Aspirin in Gestation and Reproduction" trial showed an association between the administration of 81 mg aspirin and a reduction in the rate of spontaneous preterm births in women with a history of miscarriage [9]. A recently published meta-analysis also found a decrease in the rate of spontaneous preterm births in women who had an increased risk of preeclampsia and were therefore taking aspirin as prophylaxis [10].

In addition, another secondary analysis of a prospective randomized study on the prevention of preeclampsia and a prospective randomized study have provided further indications that low-dose aspirin also reduces the rate of spontaneous preterm births in low-risk women [11, 12].

## Review

### Literature search

A selective literature search in PubMed up until April 2020 was carried out using the terms "randomized trial", "randomized study", "spontaneous preterm birth", "aspirin".

### Uteroplacental ischemia as a cause of spontaneous preterm birth

After ascending infection, vascular lesions are the second most common pathohistological phenomenon reported on connected with late miscarriage or preterm birth [13, 14]. In 2006, Ball et al. investigated a possible connection between late miscarriage and absent physiological transformation of the uterine spiral arteries. The histological changes in the placental bed of 26 women who suffered late miscarriage were compared with those in 74 women who terminated their pregnancies. Endovascular trophoblasts in the spiral arteries of the myometrium were significantly reduced in patients who had a late miscarriage (4 vs. 31 %, p = 0.001) as were intramural trophoblasts (4 vs. 18 %, p = 0.01), and fibrinoid changes were less extensive (4 vs. 18 %, p = 0.01) [15].

Arias et al. reported on vascular lesions in the decidual vessels of the placental bed in 34.1 % of women with incipient preterm birth and preterm labor but no signs of rupture of membranes compared to 11.8 % of women with an uncomplicated course of pregnancy. Preterm placental abruption was observed significantly more often in women who had preterm labor (9.5 vs. 0 %; p = 0.001). Women with preterm birth due to preterm labor were more likely to have ischemic placental lesions compared to women with preterm labor who delivered at term (25.4 vs. 3.7 %, p < 0,05) [13].

In a systematic histological study, Kim et al. compared the placental bed of women who delivered at term with that of wom-

en who had preterm birth and preterm labor and women with preeclampsia. The percentage of spiral arteries in the myometrium with failure of physiological transformation was significantly higher in women with preterm birth (30.9 vs. 13.6%, p = 0.004) compared to women who delivered at term. This also applied to the decidual segment of the spiral arteries (13.1 vs. 3.6%, p = 0.001) [16]. Similar findings were also reported for patients who had preterm birth and preterm rupture of membranes [17]. In contrast to this, however, the failure of transformation of the uterine spiral arteries in patients with preeclampsia was much higher (80.5 and 33.1%) [16]. Why failure of transformation leads to preeclampsia in some women while other women "only" have preterm labor is still unknown. It is possible that the extent of ischemia in the resulting lesion plays a decisive role [18].

There is ample evidence that ischemic uteroplacental lesions induce preterm labor:

1. Studies of primates have shown that chronic occlusion of uterine blood flow can induce preterm birth due to preterm labor [19].
2. Placental abruption occurs more commonly in women with preterm birth and preterm labor/preterm rupture of membranes compared to women who deliver at term [13, 20 – 22].
3. Women who go into preterm labor and have pathological uterine Doppler findings have a significantly higher preterm birth rate compared to women with normal Doppler findings [23].
4. The incidence of fetuses with growth retardation is higher for women who have a preterm birth after preterm labor/preterm rupture of membranes [24 – 29].
5. The plasma concentration of anti-angiogenic factors is higher in women who have a preterm birth because of preterm labor compared to women who deliver at term despite preterm labor [30, 31].

## Aspirin

Aspirin is classified as an NSAID (nonsteroidal anti-inflammatory drug) and has an inhibitory effect on the two major isoforms of the enzyme cyclooxygenase (COX-1 and COX-2). COX-1 and COX-2 enable the biosynthesis of prostaglandins. COX-1 is located in the vascular endothelium where it regulates the production of prostacyclin und thromboxane $A_2$, i.e. prostaglandins with opposing effects on vascular homeostasis and thrombocyte function. Prostacyclin is a potent vasodilator and inhibits thrombocyte function, whereas thromboxane $A_2$ is a potent vasoconstrictor and promotes thrombocyte aggregation. The COX-2 isoform is inducible and is expressed almost exclusively after the release of cytokines or other mediators of inflammation. The effect of aspirin on COX-dependent prostaglandin synthesis depends on the dose. Low doses (60–150 mg/day) of aspirin lead to irreversible acetylation of COX-1 which leads to decreased synthesis of thromboxane $A_2$ in thrombocytes but without affecting prostacyclin synthesis in the endothelium [32, 33]. At higher concentrations, aspirin inhibits both COX-1 and COX-2 and thus all prostaglandin synthesis [8]. It is therefore quite conceivable that low-dose aspirin could counteract uteroplacental ischemia, reducing the associated release of prostaglandins and preventing potential spontaneous preterm birth.

### Aspirin – maternal risks

The majority of systematic reviews of randomized controlled trials found no increase in bleeding complications following the administration of low-dose aspirin in pregnancy [6, 34, 35]. A USPSTF report on the prevention of preeclampsia with low-dose aspirin observed no increase in preterm placental abruption (11 studies, 23 332 pregnant women, RR 1.17; 95% CI: 0.93–1.48), postpartum bleeding (9 studies, 22 760 pregnant women, RR 1.02; 95% CI: 0.96–1.09) or median blood loss (5 studies, 2478 pregnant women, RR not calculated) [35]. Daily long-term aspirin intake by non-pregnant women (< 300 mg/daily for > 5 years) was associated with an increased risk of major gastrointestinal and cerebral bleeding [36]. A randomized controlled study of pregnant women who took low-dose aspirin for preeclampsia prophylaxis found a slightly higher risk for transfusions in the group of women who took aspirin (4.0 vs. 3.2%) [7].

### Fetal risks

A number of systematic reviews of studies in which low-dose aspirin was administered to prevent preeclampsia found no increased risk of congenital malformations [6, 34, 35]. In addition, a randomized controlled study of 1228 women, 615 of whom had already begun taking aspirin prior to conception and then continued to take aspirin during pregnancy, found no increased risk of negative effects on fetuses and neonates [37].

The number of congenital malformations in a cohort of just under 15 000 pregnant women who took aspirin in the first trimester of pregnancy was also not higher [38]. Nevertheless, suspicions have been voiced about a possible association between aspirin intake and the occurrence of gastroschisis [39 – 41]. A meta-analysis of 5 case-control studies showed that a history of aspirin consumption was associated with a twofold higher risk of gastroschisis [42]. These findings should, however, be interpreted with great caution, primarily because the recall bias should not be underestimated. The analysis also did not include information about aspirin doses or other medications taken.

Low-dose aspirin intake (60–150 mg) in the 3rd trimester of pregnancy is not associated with premature occlusion of Botalli's duct [43, 44]. A Cochrane review found no increased risk of neonatal intracranial bleeding (10 studies, 26 184 infants) or other neonatal bleeding complications (8 studies, 27 032 infants) [6]. Analysis of the pooled data in the systematic review of the USPSTF also found no increase in intracerebral bleeding complications in neonates (10 RCTs, 22 158 pregnant women; RR 0.84; 95% CI: 0.61–1.16) [35].

## Aspirin for the prevention of preeclampsia and fetal growth restriction

A meta-analysis on the prevention of preeclampsia using aspirin was published in 2018, which included 16 studies with 18 907 patients. Eight of the studies were high-quality studies. Data heterogeneity was very low ($I^2 = 0\%$) in the studies which used higher aspirin doses (≥ 100 mg) and began aspirin administration in early pregnancy (≤ 16 weeks of gestation [GW]). The administration of aspirin significantly reduced the rate of early preeclampsia in this subgroup (RR 0.33; 95% CI: 0.19–0.57). An impact on the preeclampsia rate in women who delivered at term could not be con-

firmed [3]. The prophylactic administration of aspirin before 16 weeks of gestation significantly reduced the rate of fetuses with growth retardation; the reduction was dose dependent (75 mg aspirin: RR 0.48, 95% CI: 0,32–0.72; 150 mg aspirin: RR 0.29, 95% CI: 0.10–0.82) [4].

The efficacy of aspirin in preventing preeclampsia and fetal growth restriction is apparently significantly dependent on when aspirin therapy is started. The physiological transformation of the uterine spiral arteries is concluded between 16 and 18 weeks of gestation [45]. Aspirin intake will therefore only affect preeclampsia-induced changes to the transformation process if administration is started very early.

## Aspirin for the prevention of spontaneous preterm birth in high-risk patients

Quite early on, it was already conjectured that the prophylactic administration of aspirin could also reduce the rate of preterm births. In a meta-analysis published in 2007, Duley reported a decrease in the incidence of preterm births of 8% (RR 0.92, 95% CI: 0.88–0.97) [6]. It was initially thought that this decrease was due to the prevention of iatrogenic preterm births.

More recent studies now indicate that aspirin may also reduce the rate of spontaneous preterm births. Silver et al. carried out a secondary analysis of the "Effects of Aspirin in Gestation and Reproduction" trial [9, 46]. In this study, women who had had a miscarriage before 20 weeks of gestation in the previous 12 months received 81 mg aspirin as prophylaxis. The inclusion criteria were later changed to include up to 2 late miscarriages, irrespective of gestational age and the timepoint of randomization. The preterm birth rate with aspirin was 4.1% (22/535), which was slightly lower than placebo (5.7%; 31/543); however, the difference was not statistically significant (RR 0.72; 95% CI: 0.42–1.23). The trend was also observed for the rate of spontaneous preterm births (1.1 vs. 2.2%; RR 0.51; 95% CI: 0.19–1.34) (▶ **Table 3**). However, when data analysis only included those patients in the study who were enrolled using the original inclusion criteria, then the preterm birth rate in the group of women treated with aspirin was significantly lower (RR 0.39; 95% CI: 0.16–0.94) [9].

In a secondary analysis of a prospective randomized multicenter study, Abramovici et al. also found indications that the administration of 60 mg aspirin reduced the rate of spontaneous preterm births [47, 48]. The investigated patients had a high risk of preeclampsia. Inclusion criteria were: insulin-dependent diabetes prior to pregnancy, chronic hypertension, multiple pregnancy, and preeclampsia in a previous pregnancy. The intervention was started between 13 und 26 weeks of gestation. Abramovici et al. additionally stratified the groups according to smokers and non-smokers. Aspirin significantly reduced the rate of spontaneous preterm births before 37 weeks of gestation (25.0 vs. 30.2%; RR 0.83, 95% CI: 0.73–0.94) and before 32 weeks of gestation (6.4 vs. 8.9%; 0.72, 95% CI: 0.55–0.94) in the group of non-smokers [47] (▶ **Table 3**).

In 2017, van Vliet et al. published a meta-analysis on the effect of low-dose aspirin intake (60–150 mg) on the rate of spontaneous preterm births. They used the datasets of a previous meta-analysis which had investigated the effect of low-dose aspirin on the prevention of preeclampsia in high-risk patients (The Perinatal Antiplatelet Review of International Studies Individual Participant Data [34]). Conditions considered to be high risk included: status post (s/p) preeclampsia, s/p pregnancy-induced hypertension, s/p fetal growth restriction, preexisting maternal disease (kidney damage, diabetes, immune disease, chronic hypertension), primiparity, multiple pregnancy, etc. The data of 28 797 patients from 17 studies for whom information about the delivery mode was available (spontaneous vs. iatrogenic preterm birth) were included in the final analysis. Aspirin intake caused a decrease in the rate of spontaneous preterm births before 37 weeks (RR 0.93; 95% CI: 0.86–0.996) and before 34 weeks of gestation (RR 0.86; 95% CI: 0.76–0.99) (▶ **Table 3**). The trend was even apparent before 28 weeks of gestation (RR 0.81; 95% CI: 0.59–1.12). The reduction in the rate of spontaneous preterm births was only apparent in the group of women who had had a previous pregnancy (RR 0.83; 95% CI: 0.73–0.95) but not in the group of primiparous women (RR 0.98; 95% CI: 0.89–1.09) [10].

## Aspirin for the prevention of spontaneous preterm birth in low-risk patients

Indications that aspirin also reduces the rate of spontaneous preterm births in low-risk patients would be important for obstetric management. In 2018, Andrikopoulou et al. published a secondary analysis on this issue, based on the data of a prospective, randomized multicenter study [11, 49]. The datasets used in their analysis were obtained from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Network. The original multicenter study investigated the impact of 60 mg aspirin on the incidence of preeclampsia in low-risk women. The women enrolled in the study were primiparous women without prior medical conditions. The intervention was started between 13 and 25 weeks of the pregnancy [49]. The secondary analysis showed a significant reduction in the rate of spontaneous preterm births before 34 weeks (1.03 vs. 2.34%; RR 0.46, 95% CI: 0.23–0.89) in the women receiving aspirin [11] (▶ **Table 1**). It must be noted, however, that the primary data date back to the 1990s and that perinatal standards in those days simply did not reflect current standards. However, these data are valuable to generate hypotheses.

The data from ASPIRIN trial, a randomized, prospective, double-blinded, placebo-controlled multicenter study, point in the same direction. A total of 11 976 primiparous women without prior medical conditions from six countries (India, Democratic Republic of the Congo, Guatemala, Kenya, Pakistan and Zambia) who were between 6 + 0 weeks and 13 + 6 weeks of their pregnancy were recruited into the study. Gestational age was determined using early ultrasound scans. The women in the intervention group received 81 mg aspirin per day up to 36 + 6 weeks or delivery of the infant. The primary study outcome was preterm birth before 37 weeks of gestation. The data were evaluated based on a modified intention-to-treat protocol. The results for 5990 women in the intervention group and 5764 women in the placebo group were included in the final analysis. The administration of aspirin significantly reduced the rate of preterm births before 37 weeks (11.6 vs. 13.1%; RR 0.89; 95% CI: 0.81–0.98, p = 0.012) (▶ **Table 2**). A decrease in perinatal mortality (RR 0.86; 95% CI: 0.74–1.00, p = 0.048), early preterm birth before

▶ **Table 1** Effect of 60 mg aspirin on the overall preterm birth rate and the rate of spontaneous preterm births [11].

| Variables | Aspirin (n = 1262) | Placebo (n = 1281) | aOR (95 % CI) |
|---|---|---|---|
| Spontaneous preterm birth < GW 34 | 13 (1.03 %) | 30 (2.34 %) | 0.46 (0.23–0.89) |
| All preterm births < GW 34 | 20 (1.58 %) | 33 (2.58 %) | 0.62 (0.35–1.12) |
| spontaneous preterm births < GW 37 | 83 (6.58 %) | 90 (7.03 %) | 0.97 (0.71–1.33) |
| All preterm births < GW 37 | 99 (7.84 %) | 105 (8.20 %) | 0.97 (0.72–1.31) |

aOR: adjusted odds ratio for body mass index, ethnic affiliation, smoking, marital status, level of education; 95 % CI: 95 % confidence interval

▶ **Table 2** Primary and secondary study outcomes of the ASPIRIN trial [12].

| | Aspirin | Placebo | RR (95 % CI) | p-value |
|---|---|---|---|---|
| **Primary study outcome** | | | | |
| Preterm birth < GW 37 | 668/5780 (11.6 %) | 754/5764 (13.1 %) | 0.89 (0.81–0.98) | 0.012 |
| **Secondary maternal study outcome** | | | | |
| Hypertension | 352/5780 (6.1 %) | 325/5764 (5.6 %) | 1.08 (0.94–1.25) | 0.299 |
| Preterm birth < GW 34 and hypertension | 8/5780 (0.1 %) | 21/5764 (0.4 %) | 0.38 (0.17–0.85) | 0.015 |
| **Secondary fetal study outcome** | | | | |
| Small for gestational age | 1506/5492 (27.4 %) | 1564/5467 (28.6 %) | 0.95 (0.90–1.01) | 0.171 |
| Perinatal mortality | 264/5779 (4.57 %) | 309/5763 (5.36 %) | 0.86 (0.73–1.00) | 0.048 |
| Preterm birth < GW 34 | 189/5780 (3.3 %) | 230/5764 (4.0 %) | 0.75 (0.61–0.93) | 0.039 |
| Preterm birth < GW 28 | 54/5780 (0.9 %) | 75/5764 (1.3 %) | 0.72 (0.51–1.02) | 0.062 |
| Spontaneous miscarriage | 134/5956 (2.25 %) | 152/5964 (2.56 %) | 0.88 (0.70–1.10) | 0.261 |
| Stillbirth | 141/5780 (2.44 %) | 166/5764 (2.88 %) | 0.85 (0.68–1.06) | 0.141 |

RR: relative risk; 95 % CI: 95 % confidence interval. The effect of 81 mg aspirin/day, starting before 14 weeks of gestation, on the preterm birth rate of primiparous women without prior medical conditions was investigated.

34 weeks of gestation (RR 0.75; 95 % CI: 0.61–0.93, p = 0.039) and in the incidence of women who gave birth before 34 weeks with pregnancy-induced hypertension/preeclampsia (RR 0.38; 95 % CI: 0.17–0.85, p = 0.015) was also observed [12] (▶ **Table 2**).

Unfortunately, the study did not differentiate between spontaneous and iatrogenic preterm birth. But as there were no significant differences in the causes of iatrogenic preterm birth (maternal hypertension, fetal growth restriction) between groups, it can be presumed that aspirin reduced the rate of spontaneous preterm births [12].

When interpreting the results of the trial, it is important to be aware that perinatal mortality was about 5 %, reflecting a level of obstetric care which cannot be compared with that of Germany [12]. We will have to await the results of the APRIL trial. This Dutch study is investigating the impact of 80 mg aspirin on the spontaneous preterm birth rate of women with a prior history of spontaneous preterm birth [50].

## Conclusion

As demonstrated in a number of recent studies, indications that the administration of low-dose aspirin does not just reduce the incidence of preeclampsia and fetal growth restriction but also the rate of spontaneous preterm births are increasing. This is unsurprising as these clinical pathologies appear to share a common pathophysiological pathway.

Depending on the results of studies which will be published in the coming few years, there is likely to be a new discussion about the prophylactic administration of aspirin to all pregnant women, starting at the latest in 12 weeks of gestation. Generally administering aspirin would be justifiable in view of the very low side effects for mother and child and would have the advantage that expensive screening tools (e.g. different methods used for preeclampsia screening) would become obsolete because they would no longer be of importance for treatment decisions.

### Conflict of Interest

The authors declare that they have no conflict of interest.

▶ **Table 3** Studies on administration of aspirin to prevent spontaneous preterm births.

| Studies | Number of patients (N) | Patient characteristics | Aspirin | | Spontaneous preterm birth rate before 37 weeks |
|---|---|---|---|---|---|
| | | | Dose | Begin | RR (95 % CI) |
| **High-risk cohort** | | | | | |
| Silver et al., 2015 [9]<br>Secondary analysis of [46] | 1 078 | s/p miscarriage < GW 20 | 81 mg | Prior to conception | 0.51 (0.19–1.34) |
| Abramovici et al., 2015 [47]<br>Secondary analysis of [48] | 2 500 | insulin-dependent diabetes prior to pregnancy, chronic hypertension, multiple pregnancy, s/p preeclampsia | 60 mg | GW 13–26 | 0.83 (0.73–0.94)[+] |
| Vliet et al., 2017 [10]<br>Secondary analysis of [34] | 28 797 | s/p preeclampsia, s/p pregnancy-induced hypertension, s/p fetal growth restriction, preexisting maternal disease (kidney damage, diabetes, immune disease, chronic hypertension), primiparity, multiple pregnancy, etc.) | 60–150 mg | GW 12–32 | 0.93 (0.86–0.996) |
| **Low-risk cohort** | | | | | |
| Andrikopoulou et al., 2018 [11]<br>Secondary analysis of [49] | 2 543 | primiparous women without comorbidities | 60 mg | GW 13–25 | 0.46 (0.23–0.89)[*] |
| Hoffman et al., 2020 [12] | 11 976 | primiparous women without comorbidities | 81 mg | GW 6–13 | 0.89 (0.81–0.98)[**] |

RR: relative risk; 95 % CI: 95 % confidence interval. [+] in non-smokers, [*] rate of spontaneous preterm births < GW 34, [**] preterm birth rate < GW 37

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