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# Aspirin can prevent Miscarriages

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## Abstract

Recurrent miscarriages are post implantation failures in natural conception; they are also termed as habitual abortions or recurrent pregnancy losses. Recurrent pregnancy loss is disheartening to the couple and to the treating clinician. There has been a wide range of research from aetiology to management of recurrent pregnancy loss. It is one of the most debated topics among clinicians and academics. The ideal management is unanswered. This review is aimed to produce an evidence-based guidance on clinical management of recurrent miscarriage. The review is structured to be clinically relevant. The aim of this study was to assess the value of low dose aspirin (100 mg daily) in improving the subsequent live birth rate amongst women with either unexplained recurrent early miscarriage (<13 weeks gestation) or unexplained late pregnancy loss ($n$ = 39). Amongst women with recurrent early miscarriages, there was no significant difference in the live birth rate between those who took aspirin (39/38; >88% compared with those who did not take aspirin. This relationship was independent of the number of previous early miscarriages. In contrast, women with a previous late miscarriage who took aspirin had a significantly higher live birth rate (30/44; 64.6%) compared with those who did not take aspirin (30/61; 49.2%: OR 1.88; 95% CI 1.04–3.37). The empirical use of low dose aspirin amongst women with unexplained recurrent early miscarriage is not justified. We are currently investigating the role of incremental doses of aspirin in the treatment of women both with early miscarriages associated with thrombophilic abnormalities and in those with late pregnancy losses. Recurrent miscarriages are post implantation failures in natural conception; they are also termed as habitual abortions or recurrent pregnancy losses. Recurrent pregnancy loss is disheartening to the couple and to the treating clinician. There has been a wide range of research from aetiology to management of recurrent pregnancy loss. It is one of the most debated topics among clinicians and academics. The ideal management is unanswered. This review is aimed to produce an evidence-based guidance on clinical management of recurrent miscarriage. The review is structured to be clinically relevant.

**Keywords:** aspirin, miscarriages, live birth rate, pregnancy loss.

## Introduction

Spontaneous miscarriage is a major loss for all pregnant women. It affects 1% of all women.[1] The incidence of spontaneous miscarriage may be much greater than is clinically recognized. Spontaneous miscarriage occurs in 12% to 15% of all pregnancies. Thirty percent pregnancies are lost between implantation and sixth week.

Maternal age and previous miscarriages increase risk of subsequent miscarriages. [2]The management of recurrent miscarriages is an unsolved problem; up to 50% of cases of recurrent losses will not have a clearly defined etiology. The investigations and management of recurrent miscarriages is one of the most debated

topics. This review is aimed to provide evidence-based approach to manage recurrent pregnancy loss. This review is structured to be clinically relevant. Pregnancy is a hypercoagulable state. Over the last decade evidence has accumulated to suggest that some cases of recurrent miscarriage and later pregnancy complications are due to an exaggerated haemostatic response during pregnancy leading to placental thrombosis and infarction. First, microthrombi are a common finding in the placental vasculature of women with recurrent miscarriage (Rushton, 1988); secondly, placental thrombosis has been described in association with individual thrombophilic defects (Rai *et al*., 1996; Dizon *et al*., 1997); and finally, there is an increased prevalence of both congenital and acquired thrombophilic defects amongst women with adverse pregnancy outcome at all gestational ages (Rai *et al*., 1995; Preston *et al*., 1996; Kupferminc *et al*., 1999).Low dose aspirin is an anti-platelet agent which irreversibly inhibits platelet cyclo-oxigenase and thereby decreases the production of thromboxane A2 (TXA2), a potent vasoconstrictor. Aspirin has been widely used in attempts to treat pregnant women with recurrent miscarriage associated with antiphospholipid antibodies (aPL), an acquired thrombophilic defect, and other auto-immune conditions (Kutteh, 1996; Laskin *et al*., 1997; Rai *et al*., 1997). The aim of this study was to assess the value of low dose aspirin in improving the subsequent livebirth rate amongst women with either unexplained recurrent early miscarriage or unexplained late pregnancy loss.

## Materials and Methods

### Subjects

An observational study of the prospective pregnancy outcome of 1055 women who had a history of either (i) three or more consecutive early miscarriages (<13 weeks gestation; $n$ = 805) or (ii) at least one late miscarriage (>13 weeks gestation; $n$ = 250) was performed (Table I). All women were investigated according to our protocol and no causes for their pregnancy losses were found (Clifford *et al*., 1994). In brief, all women had a normal peripheral blood karyotype, as did their partner, (ii) normal uterine anatomy demonstrated on ultrasound and (iii) persistently negative tests for aPL (lupus anticoagulant and anticardiolipin antibodies). All women conceived spontaneously and only singleton pregnancies were studied[3] . We have used different keywords and MeSH terms to generate set of results with were combined to generate most relevant results. The evidence was searched using individual subclass of etiology of recurrent pregnancy loss. Different key words were used such as recurrent miscarriage, recurrent pregnancy loss, habitual abortions, pregnancy failures, unexplained, and idiopathic miscarriage; and these words were combined with various factors known to cause or treat miscarriages. The search results were combined and most relevant results were grouped together for critical appraisal. The evidence was sought for all current recommendations as well as all unanswered questions on investigating and managing recurrent miscarriages. The good-quality meta-analysis was critically appraised and accepted. The recommendations are based on evidence. The evidence is graded as (I-IV).

I. High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a very low risk of bias
II. Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a high risk of bias or high-quality case–control or cohort studies
III. Well-conducted case–control or cohort studies with risk of confounding, bias
IV. Nonanalytical studies, e.g. case reports, case series
V. Expert opinion

### Management during pregnancy

Women were divided into two groups—those who chose to take low dose aspirin (100 mg daily) and those who did not take aspirin. Aspirin was started within 5 weeks of amenorrhea and continued until delivery. Both groups of women took folic acid (400 µg daily) until 14 weeks gestation as prophylaxis against neural tube defects. No woman took heparin[2]. All were encouraged to attend a dedicated early pregnancy

clinic at which supportive care was offered and serial first trimester ultrasound scans were performed[4]. Our OBS/GYNAE OPD is a state referral centre. Accordingly, the overwhelming majority of women that we see have been previously counseled by a variety of doctors—both general practitioners and gynecologists. Many of these individuals recommend aspirin treatment on an empirical basis[5]. One of the primary aims of this study was to provide data in order that clinicians may have some basis, or lack of basis, for recommending aspirin therapy during pregnancy.

## Results

Women with unexplained recurrent early miscarriages had a good chance of a subsequent successful pregnancy (Table II). There was no significant difference in the livebirth rate between those who took aspirin (251/367; 68.4%) compared with those who did not take aspirin [278/438; 63.5%; odds ratio (OR) 1.24; 95% confidence interval (CI) 0.93–1.67][8]. This relationship was independent of the number of previous early miscarriages (Figure 1). In contrast, women with a previous late miscarriage who took aspirin had a significantly higher livebirth rate (122/189; 64.6%) compared with those who did not take aspirin (30/61; 49.2%: OR 1.88; 95% CI 1.04–3.37)(Table III). There was no significant difference in either the gestational age at delivery or the birthweight between those taking aspirin and those not taking aspirin (Tables II and III). No baby had a congenital abnormality. The median gestational age of miscarriage amongst women with a previous late miscarriage who took aspirin was 14.6 weeks (range 5.2–22.8) compared with 8.9 weeks (range 5.6–18.4) amongst those who did not take aspirin ($P < 0.001$). Amongst women with recurrent early miscarriage, karyotypic analysis of the products of conception was successfully undertaken in 34 women taking aspirin who miscarried (34/116; 29%) and 61 women not taking aspirin who miscarried (61/160; 38%: not significantly different)[6]. There was no significant difference in the incidence of karyotypically abnormal pregnancies between those taking aspirin (15/34; 44%) and those not taking aspirin (22/61; 36%).

**Table I.** Demographic details

| | Aspirin | No aspirin |
|---|---|---|
| **Early Miscarriage: <13 Weeks gestation.** | | |
| **There were no significant differences between the groups.** | | |
| Recurrent early miscarriages only (Number) | 367 | 438 |
| Median age (Range; Years) | 34 (20–45) | 34 (20–46) |
| Median number of previous | | |
| Miscarriages (Range) | 3 (3–14) | 3 (3–14) |
| Previous live birth | 171 (46.6%) | 179 (40.9%) |
| Previous late miscarriage (Number) | 189 | 61 |
| Median age (Range; Years) | 33 (20–43) | 34 (21–44) |
| Median number of previous late miscarriages (Range) | 1 (1–3) | 1 (1–3) |
| Previous live birth | 107 (56.6%) | 32 (52.4%) |

**Table II.** Future pregnancy outcome of women with unexplained recurrent early miscarriage

| | **Aspirin (*N* = 367)** | **No aspirin (*N* = 438)** |
|---|---|---|
| **Early miscarriage: <13 Weeks gestation.** | | |
| **There were no significant differences between the groups.** | | |
| Live birth (%) | 251 (68.4) | 278 (63.5) |
| Median gestational age at delivery | 39.6 (27–41.8) | 39.5 (30.1–41.8) |
| (Range; Weeks) | | |
| Median birth weight at delivery | 3.4 (0.8–5.0) | 3.4 (1.4–4.8) |
| (Range; Kg) | | |
| Miscarriage (%) | 116 (31.6) | 160 (36.5) |
| Early miscarriage (%) | 108 (93.1) | 153 (95.6) |
| Late miscarriage (%) | 8 (6.9) | 7 (4.4) |

**Table III** Future pregnancy outcome of women with unexplained late miscarriage

| **Aspirin (*N* = 61)** | **No aspirin (*N* = 189)** | ***P* Value** | |
|---|---|---|---|
| **Early miscarriage: <13 weeks gestation.** | | | |
| **NS = Not significant.** | | | |
| Live birth (%) | 122 (64.6) | 30 (49.2) | 0.03 |
| Median gestational age at | 38.6 (24.1–42.3) | 38.4 (26.1–41.1) | NS |
| Delivery (range; weeks) | | | |
| Median birth weight at | 3.4 (0.55–4.45) | 3.22 (0.86–4.2) | NS |
| Delivery (Range; Kg) | | | |
| Miscarriage (%) | 67 (35.4) | 31 (50.8) | |
| Early miscarriage (%) | 29 (43.3) | 26 (83.9) | |
| Late miscarriage (%) | 38 (56.7) | 5 (16.1) | < 0.001 |

## Discussion

Low dose aspirin significantly improves the livebirth rate amongst women with a previous late miscarriage. It is, however, of no benefit to those women with unexplained recurrent early miscarriages. Aspirin inhibits the action of the enzyme cyclo-oxygenase and thereby suppresses the production of TXA2 in platelets. In vascular cell walls, cyclo-oxygenase is also responsible for the conversion of arachidonic acid to prostacyclin (PGI2). TXA2 induces platelet aggregation and vasoconstriction, whilst PGI2 inhibits platelet aggregation and induces vasodilatation[7]. Women with a history of recurrent early miscarriage in weeks 4–7 of gestation have an excess of TXA2 production and between weeks 8–11 they are relatively PGI2 deficient, compared with women with no previous history of pregnancy loss (Tulpalla *et al*., 1991). These changes are greatest amongst those whose pregnancies end in miscarriage. The shift in the TXA2:PGI2 ratio, in favour of TXA2, may lead to vasospasm and platelet aggregation in the trophoblast, causing the development of microthrombi and placental necrosis. In a small study of women with early miscarriages it was reported that whilst aspirin corrects these biochemical abnormalities, it does not affect the miscarriage rate (Tulppala *et al*., 1997). There are several possible reasons for the lack of efficacy of low dose aspirin in improving the pregnancy outcome of women with recurrent early miscarriages.

First, a proportion of women with recurrent early miscarriages have lost three consecutive pregnancies purely by chance alone and have no underlying pathological abnormality; second, aspirin may truly have no effect; third, the dose of aspirin may be too low; and finally aspirin may only be of benefit to a subgroup of women with recurrent early miscarriage associated with a thrombophilic defect. Indeed, randomized controlled studies have only shown aspirin to be of benefit to women with aPL, which are an acquired thrombophilic defect (Kutteh, 1996; Rai *et al*., 1997). In this study, women took a low dose of aspirin (75 mg daily). This dose of aspirin, or an even lower dose of 60 mg daily, has often been used in pregnancy studies examining the effect of aspirin on the incidence of pre-eclampsia (CLASP Collaborative Group, 1994; Sibai, 1998). This dose derives from studies examining the effect of aspirin on myocardial re-infarction rates. In these cardiovascular studies, lower doses of aspirin (60–150 mg/day) were found to be as effective as higher doses (up to 1000 mg/day) with fewer side-effects (Antiplatelet Trialists' Collaboration, 1994a) [9]. This may not be the case in pregnancy, and indeed the mechanisms underlying the cardio-protective effects of aspirin may not be applicable to pregnancy[1]. In contrast to its lack of efficacy amongst women with unexplained recurrent early miscarriage, low dose aspirin significantly increased the prospective livebirth rate amongst women with a previous late miscarriage. This supports the hypothesis that a number of cases of second trimester miscarriage and later pregnancy complications have a thrombotic aetiology. An important finding, which demands further investigation, was the significantly higher number of late miscarriages amongst women who took aspirin compared with those who did not. An explanation for this may lie in our understanding of the development of placental intervillous blood flow. Clearly, in order for maternal thrombophilic defects to cause placental thrombosis and subsequent pregnancy loss, there must be a maternal intervillous circulation. Recent histological data suggest that this only develops after 8 weeks gestation (Burton *et al*., 1999). Amongst women who had a further late miscarriage, aspirin at a dose of 75 mg daily may be sufficient to maintain the pregnancies until after 14 weeks gestation, but insufficient to maintain them to the stage of viability[10]. It is possible that higher doses of aspirin may lead to a higher livebirth rate. Whilst no study has examined the effect of variable dose aspirin in the treatment of women with recurrent miscarriage, a study on aspirin and pre-eclampsia reported excellent livebirth rates amongst those in whom the dose of aspirin was titrated during pregnancy against the mean platelet volume (Sullivan *et al*., 1998).

## Conclusion

There is now convincing evidence that many cases of recurrent miscarriage and later pregnancy complications have a thrombotic aetiology. Whilst the empirical use of low dose aspirin in women with unexplained recurrent early miscarriage cannot be justified, the role of higher doses of aspirin in the treatment of both women with early miscarriages associated with thrombophilic abnormalities and in those with late pregnancy losses.

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