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Original article

# Placental Dysfunction Disorders After Prior Miscarriages In a Sample of Iraqi Womens

D.DalyaThamer Ahmad*

*Affiliation:*
College of medicine, Al – Iraqia University, Adhamiyah, Baghdad, Iraq

**The name of the department(s) and institution(s) to which the work should be attributed:**
College of medicine, Al – Iraqia University, Adhamiyah, Baghdad, Iraq

**Address reprint requests to**
**Dr.D.DalyaThamer Ahmad**
College of medicine, Al–Iraqia University, Adhamiyah, Baghdad, Iraq or at d.alimohamad11@gmail.com

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## ABSTRACT:

**Objective:** The aim of this study was toinvestigate the association between prior miscarriages and the risks of placental dysfunction disorders, including preeclampsia, stillbirth, birth of a small for gestational age (SGA) infant, placental abruption, and spontaneous preterm birth.
**Study Design:** In a population-based cohort study including 72 primiparous women, we estimated risks of placental dysfunction disorders for women with 1 (n = 24 ), 2 (n = 20 ) and 3 or more (n = 18 ) self-reported prior miscarriages. Risks were calculated as odds ratios by unconditional logistic regression analysis and adjustments were made for maternal age, early pregnancy body mass index, smoking habits, years of formal education, *in vitro* fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis and fetal sex .
**Results:** Compared with women with no prior miscarriage, women with 1 prior miscarriage had almost no increased risks. Women with 2 prior miscarriages had increased risks of spontaneous preterm birth, preterm (<37 weeks) SGA infant, and placental abruption. The rates of all disorders were higher for women with 3 or more prior miscarriages compared with women without prior miscarriages: preeclampsia, 50% *vs* 30%; stillbirth, 22.22 % *vs* 0%, SGA infant, 22.22 % *vs* 10 %, placental abruption, 27.78 % *vs* 10 %; and spontaneous preterm birth, 27.78 % vs 10 %. The adjusted odds ratios for preterm (<37 weeks) disorders in women with 3 prior miscarriages were approximately 3.4, neonatal death, 11.11 % vs 0%.
**Conclusion:** History of 2 or more miscarriages is associated with an increased risk of placental dysfunction disorders and should be regarded as a risk factor in antenatal care

KEYWORDS: Intrauterine growth restriction; miscarriage; placental abruption; preeclampsia, spontaneous preterm birth; stillbirth.

## INTRODUCTION

About half of women will miscarry at least once during their lives. Research has focused on the causes of recurrent miscarriage and possible ways to prevent it[1].
Women who experience a miscarriage are not only at an increased risk of a second miscarriage, but also of complications in a subsequent pregnancy[2].

Defective deep placentation has been associated with a spectrum of complications of pregnancy including preeclampsia, intrauterine growth restriction, preterm labor, preterm premature rupture of membranes, late spontaneous abortion, and abruption placentae[3].

It seems that the currently available literature on the obstetrics and neonatal outcome of pregnancies from women with a history of recurrent miscarriage shows inconsistent results, partly because of small numbers in the studies reported, and partly because of a lack of an appropriately chosen controlled population[4].
An initial miscarriage is independently associated with adverse pregnancy outcomes[5].

A significant association exists between consecutive recurrent abortions and pregnancy complications such as placental abruption, hypertensive disorders and CS. This association

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persists after controlling for variables considered to coexist with recurrent abortions[6].

A previous miscarriage was associated with an increased risk of all-cause preterm birth. The strongest association was found with extreme preterm birth[7].

Previous spontaneous abortions and missed abortions were associated with increased risks of preterm delivery, and the risks increased with severity of preterm delivery. Previous pregnancy loss increased the risk of preterm PROM and preterm labor foremost in deliveries before 32 weeks, but was not associated with other reasons of very preterm delivery[8].

Women with a history of miscarriage reported that they feared an adverse birth outcome for themselves or their infants more frequently than women without a history of miscarriage[9].

Placental dysfunction disorders have a recurrence risk and may predispose to each other (eg, SGA in 1 pregnancy predisposes for preeclampsia in subsequent pregnancy and *vice versa*) [10,11]. This suggests that a failure of implantation/placentation could result in placental dysfunction disorders with different clinical features in successive pregnancies. This might be explained by an interaction between mothers susceptibility to placentation failure and fetal genes[12,13], which are different in subsequent pregnancies.

Vascularization of the endometrium is of main importance for successful implantation and placentation[14]. 31 Vascular endothelial growth factor (VEGF) is an important proangiogenic factor[15], 32 and increased expression of VEGF in first-trimester decidua has been associated with both miscarriage and placental dysfunction disorders[16,17]. Increased angiogenic activity and a premature onset of the maternal circulation in early placental development could result in subsequent increase in oxidative stress.

It has been hypothesized that if these disturbances are severe, this may lead to a complete failure of early placentation and miscarriage[17,18]. However, if the failure is partial, the pregnancy might remain viable but with a continued imbalance in angiogenic activity and insufficient vascular remodelling during the remaining placentation process.

Genetic studies suggest that polymorphisms in the VEGF gene are associated with both recurrent miscarriages and placental dysfunction disorders[19,20].

## MATERIALS AND METHODS

A population-based study comparing all singleton pregnancies in women without previous miscarriage and with one, two or more consecutive recurrent abortions was conducted. Deliveries occurred during the years 2013 to the end of 2014.

A Stratified analysis, using a multiple logistic regression model was performed to control for confounders.

The data was collected from women who attend the outpatient clinics including demographic data, information on reproductive history and complications during pregnancy, delivery, and the neonatal period. During the first antenatal visit, usually taking place at the end of the first trimester, the mother is interviewed about her medical and obstetric history. Information about maternal characteristics such as weight, BMI and smoking habits are also recorded.

During pregnancy, we record any complication developed at any gestational age and we follows the patient closely until delivery then we records al maternal and neonatal complications.

## STUDY POPULATION AND EXPOSURE VARIABLE

Women giving birth to their first singleton infant at 22 weeks of gestation or later during the period 2013-2015 (n=72) were included. Exposure variable was number of self-reported prior miscarriages, recorded at the first antenatal visit. Number of miscarriages was categorized into no prior miscarriage (n=10), 1 miscarriage (n=24), 2 miscarriages (n=20), and 3 or more miscarriages (n =18).

## OUTCOMES

Placental dysfunction disorders included preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth.

The clinical definition of preeclampsia during the study period was a rise in blood pressure (⩾140/90 mm Hg) combined with proteinuria (⩾0.3 g/24 hours or +1 or more on dipstick on at least 2 occasions. 28 cases of all 72 was diagnosed as preeclampsia.

Stillbirth was defined as fetal death at 28 weeks of gestation or later. Analysis of stillbirth was therefore restricted to births at 28 weeks or later. The total population when calculating risk of

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stillbirth included 72 births, and it was 8 cases only.

Being born small for gestational age (SGA) was used as a proxy for intrauterine growth restriction. SGA was defined as a birth weight below 2 SD from the mean birth weight for gestational age. Only live births were included in this analysis (still birth were excluded n=8). The total population when calculating risk of SGA included 64 births, we had 10 cases only.

Preeclampsia, stillbirth, birth of an SGA infant, and placental abruption were categorized into preterm (birth before 37 weeks of gestation) and term (birth at 37th week of gestation or later). Gestational age is assessed by the last menstrual period and ultrasound scans around the 9 week of gestation in 97% of women. If no early dating ultrasound scan was available, and the last menstrual period was not recorded accurately, we used the second trimester ultrasound scan to calculate gestational age at delivery (3%).

Spontaneous preterm birth was defined as a birth before 37 gestational weeks with a spontaneous onset; we had 14 cases out of total 72.

## COVARIATES

Information about maternal age and fetal sex was collected at delivery, whereas information about body mass index (BMI), smoking habits, level of formal education and IVF was collected from the first antenatal visit. The variables were categorized according to Table 1.

Women with chronic hypertension, pregestational diabetes, hypothyroidism, or systemic lupus erythematosus (SLE) were identified from the first antenatal visit.

## STATISTICAL METHODS

The associations between 1, 2, and 3 or more prior miscarriages on the risks of preeclampsia, stillbirth, SGA birth, placental abruption, and spontaneous preterm birth were estimated in primiparous women, using women with no prior miscarriage as reference. Odds ratios with 95% confidence intervals were calculated by unconditional logistic regression analysis with adjustments for maternal and infant characteristics. The following variables were initially included in our multiple logistic regression models: maternal age, early pregnancy BMI, smoking habits, years of formal education, IVF,chronic hypertension, pregestational diabetes, hypothyroidism, SLE and fetal sex.

## STRENGTHS AND LIMITATIONS

The major strength of our study was the population-based design, suggesting that the results from this study are generalizable to other settings. In contrast to some previous studies, we were able to control for important confounders such as maternal smoking, BMI, and IVF as well as chronic hypertension, pregestational diabetes, hypothyroidism, and SLE. Exposure was measured as self-reported miscarriages, which might be both a strength and limitation. Self-reported information made it possible to include miscarriages experienced by the women regardless of a need for specialist care and we knew the gestational age at time of miscarriage. However, we had no information about their underlying etiology.

Although one of the potential limitations is small study population, but we were able to stratify the exposure by number of miscarriages and also to study rare events like stillbirth and placental abruption and to subdivide these outcomes into preterm and term disorders.

## RESULTS

Compared with women with no prior miscarriage, women with prior miscarriages were older, had a higher BMI, and were more often smokers. Furthermore, women with prior miscarriages were slightly had shorter formal education, were more often pregnant after IVF treatment, and were more likely to have chronic hypertension, pregestational diabetes, hypothyroidism, and SLE (Table 1)

Table 1.Number of prior miscarriages by maternal characteristics.

| Maternal characteristic | n/72 | Prior miscarriages | | | |
|---|---|---|---|---|---|
| | | 0 | 1`% | 2 % | >3 % |
| Age , Years | | | | | |
| < 25 | 17 | 10 | 45.83 | 15 | 11.11 |
| 25 – 29 | 18 | 50 | 25 | 25 | 11.11 |
| 30 -34 | 17 | 30 | 12.5 | 25 | 33.33 |
| >35 | 20 | 10 | 16.67 | 35 | 44.44 |
| BMI kg/$m^2$ | | | | | |

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|---|---|---|---|---|---|
| <18.5 | 13 | 30 | 25 | 10 | 11.11 |
| 18.5 – 24.9 | 38 | 50 | 54.17 | 55 | 50 |
| 25 – 29.9 | 14 | 10 | 16.67 | 25 | 22.22 |
| >30 | 7 | 10 | 4.17 | 10 | 16.67 |
| Smoking | | | | | |
| No | 53 | 100 | 70.83 | 70 | 66.67 |
| Yes | 19 | 0 | 29.17 | 30 | 33.33 |
| Education | | | | | |
| No | 10 | 20 | 8.33 | 10 | 22.22 |
| Primary | 22 | 40 | 33.33 | 40 | 11.11 |
| Secondary | 25 | 30 | 25 | 40 | 44.44 |
| Tertiary | 15 | 10 | 33.33 | 10 | 22.22 |
| IVF | | | | | |
| No | 54 | 80 | 83.33 | 70 | 66.67 |
| Yes | 18 | 20 | 16.67 | 30 | 33.33 |
| Chronic hypertension | | | | | |
| No | 50 | 100 | 75 | 70 | 44.44 |
| Yes | 22 | 0 | 25 | 30 | 66.66 |
| Pre gestational diabetes | | | | | |
| No | 55 | 90 | 83.33 | 80 | 66.66 |
| Yes | 17 | 10 | 16.67 | 20 | 44.44 |
| Hypothyroidism | | | | | |
| No | 48 | 80 | 75 | 60 | 66.66 |
| Yes | 24 | 20 | 25 | 40 | 44.44 |
| SLE | | | | | |
| No | 71 | 100 | 100 | 100 | 94.44 |
| Yes | 1 | 0 | 0 | 0 | 5.66 |
| Fetal sex | | | | | |
| Male | 42 | 40 | 66.67 | 50 | 66.67 |
| Female | 31* | 60 | 33.33 | 55* | 33.33 |

*Twin pregnancy, both are females. BMI, body mass index; IVF, *in vitro* fertilization; SLE, systemic lupus erythematosis.

## PREECLAMPSIA AND STILLBIRTH

Compared with women with no prior miscarriage, women with 1 prior miscarriage did not have increased risks of preeclampsia (30% *vs* 33%) or stillbirth (0% *vs* 4.17%). The rates of preeclampsia and stillbirth were higher in women with 2 and those with 3 or more prior miscarriages than in women without prior miscarriage: preeclampsia (40% & 50% respectively) while rate for stillbirth (15%-22.22% respectively). When we divided the outcomes into preterm and term disorders, the associations were significant only between 3 or more miscarriages and preterm disorders (Table 2 & 3)

Table 2.Risks of preeclampsia by number of prior miscarriages.

| Prior miscarriages | Preeclampsia total | | | Preterm Preeclampsia | | | Term Preeclampsia | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Rate (%) | AOR (95% CI) | N | Rate (%) | AOR (95% CI) | N | Rate ( %) | AOR (95% CI) |
| **NO** | 3 | 30 | 1.00 | 2 | 20 | 1.00 | 1 | 10 | 1.00 |
| **YES** | | | | | | | | | |
| 1 | 8 | 33.33 | 1.1667 (0.2363- 5.7598) | 5 | 20.83 | 1.0526 (0.1678- 6.6026) | 3 | 12.5 | 1.2857 (0.1173- 14.0899) |
| 2 | 8 | 40 | 1.5556 (0.3073- 7.8731) | 7 | 35 | 2.1538 (0.3555- 13.0492) | 1 | 5 | 0.4737 (0.0265- 8.4645) |
| >3 | 9 | 50 | 2.333 (0.4535- 12.0046) | 7 | 38.89 | 2.5455 (0.4139- 15.6526) | 2 | 11.11 | 1.1250 (0.0891- 14.2022) |

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Table 3.Risks of stillbirth by number of prior miscarriages.

| Prior miscarriages | Stillbirth total | | | Preterm Stillbirth | | | Term Stillbirth | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Rate ( %) | AOR (95% CI) | N | Rate (%) | AOR (95% CI) | N | Rate (%) | AOR (95% CI) |
| **NO** | 0 | 0 | 1.00 | 0 | 0 | 1.00 | 0 | O | 1.00 |
| **YES** | | | | | | | | | |
| 1 | 1 | 4.17 | 1.3404 (0.0503- 35.7055) | 0 | 0 | 0.4286 (0.0080- 23.0764) | 1 | 4.17 | 1.3404 (0.0503- 35.7055) |
| 2 | 3 | 15 | 4.2 (0.1968- 89.6136) | 3 | 15 | 1.3404 (0.0503- 35.7055 | 0 | 0 | 0.4286 (0.0080- 23.0764) |
| >3 | 4 | 22.22 | 6.5172 (0.3156- 134.5951) | 3 | 16.66 | 4.7419 (0.2212- 101.6456) | 1 | 5.56 | 1.8 (0.067- 48.3579) |

## SMALL FOR GESTATIONAL AGE AND PLACENTAL ABRUPTION

Compared with women with no prior miscarriage, women with 1 prior miscarriage did not have increased risks of SGA (8.3% *vs* 10% ) or placental abruption (12.5% *vs* 10% ) respectively. Women with 2 prior miscarriages had slightly increased risks of preterm SGA infant and placental abruption. The rates of an SGA infant and placental abruption were higher in women with 3 or more prior miscarriages than in women without prior miscarriage: SGA (22.22%) and placental abruption (27.78%). The adjusted ORs for preterm SGA and placental abruption in women with 3 prior miscarriages were around 2 - 3.4 (Table 4 & 5).

Table 4. Risks of SGA by number of prior miscarriages.

| Prior miscarriages | SGA total | | | Preterm SGA | | | Term SGA | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Rate ( %) | AOR (95% CI) | N | Rate (%) | AOR (95% CI) | N | Rate (%) | AOR (95% CI) |
| **NO** | 1 | 10 | 1.00 | 0 | 0 | 1.00 | 1 | 10 | 1.00 |
| **YES** | | | | | | | | | |
| 1 | 2 | 8.33 | 0.8182 (0.0657- 10.1960) | 1 | 4.167 | 1.3404 (0.0503- 35.7055) | 1 | 4.167 | 0.3913 (0.0220- 6.9499) |
| 2 | 3 | 15 | 1.5882 (0.1436- 17.5620) | 2 | 10 | 2.8378 (0.1241- 64.8760) | 1 | 5 | 0.4737 (0.0265- 8.4645) |
| >3 | 4 | 22.22 | 2.5714 (0.2462-26.8526) | 3 | 16.67 | 4.7419 (0.2212-101.6456) | 1 | 5.55 | 0.5294 (0.0295- 9.4994) |

Table 5. Risks of Placental abruption by number of prior miscarriages.

| Prior miscarriages | Placental abruption total | | | Preterm Placental abruption | | | Term Placental abruption | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Rate % | AOR (95% CI) | N | Rate % | AOR (95% CI) | N | Rate % | AOR (95% CI) |
| **NO** | 1 | 10 | 1.00 | 0 | 0 | 1.00 | 1 | 10 | 1.00 |
| **YES** | | | | | | | | | |
| 1 | 3 | 12.5 | 1.2857 (0.1173- 14.0899) | 1 | 4.167 | 1.3404 (0.0503- 35.7055) | 2 | 8.33 | 0.8182 (0.0657- 10.1960) |

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|---|---|---|---|---|---|---|---|---|---|
| 2 | 3 | 15 | 1.5882 (0.1436- 17.5620) | 2 | 10 | 2.8378 (0.1241-64.8760) | 1 | 5 | 0.4737 (0.0265- 8.4645) |
| >3 | 5 | 27.78 | 3.4615 (0.3439- 34.8441) | 2 | 11.11 | 3.1818 (0.1386- 73.0326) | 3 | 16.67 | 1.8 (0.1618- 20.0286) |

## SPONTANEOUS PRETERM BIRTH

Compared with women with no prior miscarriage, women with prior miscarriages had an increased risk of spontaneous preterm birth. The rates of spontaneous preterm births for women with no prior miscarriage, 1, 2 and 3 or more prior miscarriages were 10 %, 16.67 %, 20 %, and 27.78 %, respectively. (Table 6), the same result for intrauterine growth restriction, the rate is 10%, 16.67 %, 25 % and 33.33% respectively and neonatal death the rate is 0 % , 4.167 %, 10 % and 11.11 % respectively (Table 7 & 8 ).

Table 6. Risks of Spontaneous preterm birth by number of prior miscarriages.

| Prior miscarriages | Total Spontaneous preterm birth | | |
|---|---|---|---|
| | N | Rate ( %) | AOR (95% CI) |
| **NO** | 1 | 10 | 1.00 |
| **YES** | | | |
| 1 | 4 | 16.67 | 1.8 (0.1754 - 18.4686) |
| 2 | 4 | 20 | 2.25(0.2170 - 23.3246) |
| >3 | 5 | 27.78 | 3.4615 (0.3439 - 34.8441) |

Table 7. Risks of IUGR by number of prior miscarriages.

| Prior miscarriages | IUGR | | |
|---|---|---|---|
| | N | Rate (%) | AOR (95% CI) |
| NO | 1 | 10 | 1.00 |
| YES | | | |
| 1 | 4 | 16.67 | 1.8(90.1754- 118.4686) |
| 2 | 5 | 25 | 3.00(0.3006- 29.9412) |
| >3 | 6 | 33.33 | 4.5(0.4572- 44.2893) |

Table 8. Risks of Neonatal death by number of prior miscarriages.

| Prior miscarriages | NEONATAL DEATH | | |
|---|---|---|---|
| | N | Rate ( %) | AOR (95% CI) |
| **NO** | 0 | 0 | 1.00 |
| YES | | | |
| 1 | 1 | 4.167 | 1.3404 (0.0503- 35.7055) |
| 2 | 2 | 10 | 2.8378 (0.1241- 64.8760) |
| >3 | 2 | 11.11 | 3.1818 (0.1386- 73.0326) |

## DISCUSSION

In this population-based study of primiparous women, we showed that prior miscarriages were associated with increased risks of the placental dysfunction disorders preeclampsia, stillbirth, SGA birth, placental abruption, and spontaneous preterm birth. The associations were strongest for 3 or more prior miscarriages and seemed stronger for preterm placental dysfunction disorders compared with term disorders. The results support the notion that miscarriages and placental dysfunction disorders might partially share the same pathogenesis.

Placental dysfunction disorders have a recurrence risk and may predispose to each other

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(eg, SGA in 1 pregnancy predisposes for preeclampsia in subsequent pregnancy and vice versa)[10,11]. This suggests that a failure of implantation/placentation could result in placental dysfunction disorders with different clinical features in successive pregnancies[12,13].

The results in this study are in accordance with the hypothesis that miscarriage and placental dysfunction disorders have a partially common pathogenesis of early placentation failure.8 Vascularisation of the endometrium is of main importance for successful implantation and placentation[14].

This result agreed with another study done in Scotland by Bhattacharya S et al. reported that an initial miscarriage is associated with a higher risk of obstetric complications. The miscarriage group faced a higher risk of preeclampsia (adj OR 3.3, 99% CI 2.6-4.6), preterm delivery (adj OR 2.1, 99% CI 1.6-2.8) and low birth weight (adj OR 1.6, 99% CI 1.3-2.1) and preterm[21].

This result agreed with another study done in Denmark by Basso O1 et al reported that first liveborns of women in the reference cohort were compared with first liveborns in the abortion cohort, only deliveries before 34 and 37 weeks' gestation were associated with previous abortion[22].

LillTrogstad et al. investigated the effect of 3 or more miscarriages on preeclampsia, this study could not report a significant increased risk of preeclampsia, unlike our study where we find strong association between preeclampsia and previous miscarriage in a dose response manner[23].

In this study we find that there is a strong association between preterm labor and previous miscarriage with a dose response relationship , with increase number of previous miscarriage there increase in the risk of preterm labor in consistent with other study done in Scotland at 2015 by C Oliver-Williams et al.,[7] Risk increased with the number of miscarriages. Women with three or more miscarriages had the greatest risk of all-cause preterm birth (aOR 2.14; 95% CI 1.93–2.38), the same result also found by Buchmayer et al.(2004)[8], El-Bastawissi et al.,(2003)[24]; Hammoud et al.,(2007)[25]); Bhattacharya et al., (2008)[21] while in another study done by McCarthy FP et al., they found that women with two to four previous losses, but not those with a single loss, had an increased risk of spontaneous preterm birth[26].

Similar to our study, McCarthy FP et al., found that women with two to four previous losses, but not those with a single loss, had an increased risk of placental abruption (adjusted OR 2.30; 95% CI 1.36, 3.89) compared with those with no previous pregnancy or those with single loss[26].

In our study we find that one previous miscarriage is not associated with increased risk of SGA babies while 2 or more miscarriages had increased risk of SGA, this result are in accordance with a result found in a large population-based Danish study done by R.H.F. van Oppenraaij et al.[27], Other smaller studies have reported similar, although not statistically significant, increased risks of SGA in women with recurrent miscarriages compared with controls[28,4].

This result were different from result found by Voigt M et al., they report that miscarriages are not risk factors for IUGR or SGA[29].

Unlike our study, Moreau et al.,(2005)[30]; Raatikainen et al.,(2006)[31]; Parazzini et al., (2007)[32]; Reime et al.,(2008)[33] found no relationship between previous miscarriage and neonatal death..

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