Predicting adverse obstetric outcome after early pregnancy events and complications: a review

R.H.F. van Oppenraaij1, E. Jauniaux2, O.B. Christiansen3, J.A. Horcajadas4, R.G. Farquharson5, N. Exalto1,6, and On Behalf of ESHRE Special Interest Group for Early Pregnancy (SIGEP)

1Division of Obstetrics and Prenatal Medicine, Department of Obstetrics and Gynaecology, Erasmus University Medical Center, Room Ba-226, PO Box 2040, 3000 CA Rotterdam, The Netherlands 2Academic Department of Obstetrics and Gynaecology, EGA Institute for Women’s Health, Royal Free and University College London Medical School, London, UK 3Fertility Clinic 4071, Rigshospitalet, University Hospital Copenhagen, Copenhagen, Denmark 4Instituto Valenciano de Infertilidad Foundation (FIVI), University of Valencia, Valencia, Spain 5Department of Obstetrics and Gynaecology, Liverpool Women’s Hospital, Liverpool, UK

6Correspondence address. Department of Obstetrics and Gynaecology, Division Obstetrics and Prenatal Medicine, Erasmus MC, Room Ba-226, PO Box 2040, 3000 CA Rotterdam. Tel: +31-10-703-39-17; Fax: +31-23-524-28-52; E-mail: exalto@gyn.nl

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BACKGROUND: The aim was to evaluate the impact of early pregnancy events and complications as predictors of adverse obstetric outcome.

METHODS: We conducted a literature review on the impact of first trimester complications in previous and index pregnancies using Medline and Cochrane databases covering the period 1980–2008.

RESULTS: Clinically relevant associations of adverse outcome in the subsequent pregnancy with an odds ratio (OR) > 2.0 after complications in a previous pregnancy are the risk of perinatal death after a single previous miscarriage, the risk of very preterm delivery (VPTD) after two or more miscarriages, the risk of placenta praevia, premature preterm rupture of membranes, VPTD and low birthweight (LBW) after recurrent miscarriage and the risk of VPTD after two or more termination of pregnancy. Clinically relevant associations of adverse obstetric outcome in the ongoing pregnancy with an OR > 2.0 after complications in the index pregnancy are the risk of LBW and very low birthweight (VLBW) after recurrent miscarriage and the risk of VPTD after two or more termination of pregnancy. Clinically relevant associations of adverse obstetric outcome in the ongoing pregnancy with an OR > 2.0 after complications in the index pregnancy are the risk of LBW and very low birthweight (VLBW) after a threatened miscarriage, the risk of pregnancy-induced hypertension, pre-eclampsia, placental abruption, preterm delivery (PTD), small for gestational age and low 5-min Apgar score after detection of an intrauterine haematoma, the risk of VPTD and intrauterine growth restriction after a crown-rump length discrepancy, the risk of VPTD, LBW and VLBW after a vanishing twin phenomenon and the risk of PTD, LBW and low 5-min Apgar score in a pregnancy complicated by severe hyperemesis gravidarum.

CONCLUSIONS: Data from our literature review indicate, by finding significant associations, that specific early pregnancy events and complications are predictors for subsequent adverse obstetric and perinatal outcome. Though, some of these associations are based on limited or
small uncontrolled studies. Larger population-based controlled studies are needed to confirm these findings. Nevertheless, identification of these risks will improve obstetric care.

**Key words:** first trimester complication / adverse obstetric outcome / miscarriage / recurrent miscarriage / threatened miscarriage

### Introduction

Early pregnancy events and complications are among the most common general medical complications in women during pregnancy. Most of these occur before 12 weeks of gestation and include (recent) miscarriage, vaginal bleeding, intrauterine haematoma (IUH), vanishing twin and hyperemesis gravidarum (HG). The presence of any complication can be extremely distressing for the women. For the clinician, it is important to interpret the symptoms and to understand the short- and long-term consequences of early pregnancy complications, especially for reassuring and supporting the couple at a difficult time (Lamb, 2002; Griebel et al., 2005). In particular, it is pivotal to evaluate the likelihood of subsequent adverse obstetric outcome as secondary complication and to be vigilant in screening and intervening, if possible, to avoid or reduce the anticipated detrimental effects.

Data on the link between early pregnancy complications and obstetric outcome and their possible treatment or prevention are sparse and mainly limited to retrospective small series of many different pathologies or large series describing specific pathology. This has prompted the ESHRE Special Interest Group for Early Pregnancy (SIGEP) to perform a comprehensive review of first trimester pregnancy events and complications as a precursor or indicator of late pregnancy events and beyond. Given the paucity of good quality data, this paper rests on the best available evidence rather than on a formal systematic review.

### Methods

For this review, the following conditions were included and evaluated as early pregnancy complications (presenting <12 weeks of gestation), defined as adverse clinical events in the obstetric history: previous miscarriage, recurrent miscarriage (RM, three or more miscarriages), termination of pregnancy (TOP) or complications in the ongoing pregnancy: threatened miscarriage, IUH, crown-rump length (CRL) discrepancy, vanishing twin, HG and pregnancy with an intrauterine device (IUD).

As late pregnancy sequelae, we have included: antepartum haemorrhage (APH), pregnancy-induced hypertension (PIH, blood pressure >140/90 mmHg measured twice, taken at least 6 h apart), pre-eclampsia (PE, as PIH and ≥300 mg protein in 24 h urine sample), placental abruption, placenta praevia, preterm premature rupture of membranes (PPROMs, rupture of membranes <37 weeks gestational age (GA) and more than 24 h before delivery), preterm delivery (PTD, <37 weeks GA), very preterm delivery (VPTD, <34 weeks GA), intrauterine growth restriction (IUGR, birthweight <5th percentile for GA), small for gestational age (SGA, birthweight <10th percentile for GA), and the impact on perinatal outcome including low birthweight (LBW, <2500 g), very low birthweight (VLBW, <1500 g), congenital malformations, low 5-min Apgar score (<7), intrauterine fetal death (>24 weeks GA) and perinatal death (within 30 days after delivery).

For each specific early pregnancy event and complication, we performed a systematic literature search using Medline and the Cochrane Database, covering the period between 1980 and October 2008. Free text search terms and Medical Subject Headings (MeSH) terms for each specific early pregnancy complication were combined with each late pregnancy sequel and perinatal outcome. Furthermore, we used, as an ‘umbrella’ approach, MeSH terms of each early pregnancy complication combined with pregnancy outcome and each late complication combined with aetiology or risk factors. Hereafter, reference lists of the retrieved publications were searched by hand. Excluded were studies in which (i) another language than English was used, (ii) an appropriate control group was missing (no control group present or non-comparable groups due to major differences in patient characteristics) and (iii) the early or late pregnancy complications were poorly defined or were merged.

For each study, the odds ratio (OR), favoured for retrospective cohort and case–control studies and prospective studies with multivariate analysis, or relative risks (RR), used in prospective randomized controlled trials and cohort studies, with the associated 95% confidence interval (CI), were retrieved. In this review, we did not apply formal meta-analysis as heterogeneity of data did not allow for this technique. Results were summarized in two tables. The definitions of the levels of evidence and grades of recommendation used in this review originate from the Oxford centre for evidence-based medicine (2001). The prognostic value of previous first trimester events for the subsequent index pregnancy is summarized in Table I. The prognostic value of first trimester complications for the same pregnancy is summarized in Table II.

### Previous miscarriage

A sporadic miscarriage is defined as a single or maximum two episodes of spontaneous pregnancy loss before 20 weeks GA (Farquharson et al., 2005). The overall incidence of clinical sporadic miscarriage is ~12% (Blohm et al., 2008). After a previous miscarriage, the risk of miscarriage in the subsequent pregnancy is increased to 16–20% (Regan et al., 1989; Knudsen et al., 1991).

There is in the next pregnancy after a miscarriage an increased risk of PPROM, PTD, VPTD and possibly PE. This risk increases with the number of miscarriages and these women also have an increased risk of placent al abruption, placenta praevia and SGA (Table I and Supplementary Appendix Tables A1 and A2). Possibly, the pathological mechanisms which can be attributed to miscarriage (like thrombophilia disorders, maternal immunologic and hormonal abnormalities, infection, incompetent cervix and uterine abnormalities), interpregnancy interval and treatment modality could explain some of the associations with adverse obstetric outcome (Thom et al., 1992; Sheiner et al., 2005). However, it is informative for couples to know that a small study has found that the interval to the next pregnancy and the live birth rate in the next pregnancy does not depend on the treatment modality for the miscarriage (Tam et al., 2005).
Obstetric outcome

Although a previous live birth will reduce the risk of developing PE in a subsequent pregnancy compared with nullipara, this association is not found between a single previous miscarriage and the risk of developing PE, neither in nullipara nor in multipara (Seidman et al., 1989; Eskenazi et al., 1991; Thom et al., 1992; Stone et al., 1994; Eras et al., 2000; Dempsey et al., 2003). In only one small study, a protective effect is described of having had a single previous miscarriage among multiparas (OR 0.1, 95% CI 0.0–0.5) but not among nulliparas (Eskenazi et al., 1991). In a recent well-controlled study, Bhattacharya et al. (2008) even found an increased risk of PE (OR 3.3, 95% CI 2.6–4.6) after a single miscarriage. Thom et al. (1992) did not find this increased risk (OR 1.0, 95% CI 0.8–1.3) in a larger but poorly controlled study. After two previous miscarriages, a higher incidence of severe, but not mild, PE (OR 1.5, 95% CI 1.3–1.8) is reported (Sheiner et al., 2005). A single previous miscarriage is not associated with an increased risk for placental abruption and placenta praevia (Schoenbaum et al., 1980; Thom et al., 1992; Bhattacharya et al., 2008), but after two miscarriages, the probability of placental abruption (OR 1.5, 95% CI 1.1–1.7) and placenta praevia (OR 1.7, 95% CI 1.3–2.3) is increased (Sheiner et al., 2005).

Table I Early pregnancy events and complications as risk factors for adverse obstetric outcome in the subsequent pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Previous miscarriage</th>
<th>Recurrent miscarriage</th>
<th>Termination of pregnancy</th>
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<tbody>
<tr>
<td></td>
<td>One G</td>
<td>Two or more G</td>
<td>Three or more G</td>
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<tr>
<td>Obstetric outcome</td>
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<tr>
<td>Pregnancy-induced hypertension</td>
<td>NS D</td>
<td>NS D</td>
<td>No data D</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>OR 3.3 (2.6–4.6) D</td>
<td>OR 1.5 (1.3–1.8) C</td>
<td>NS C</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>NS C</td>
<td>OR 1.5 (1.1–1.7) C</td>
<td>NS C</td>
</tr>
<tr>
<td>Placenta praevia</td>
<td>NS C</td>
<td>OR 1.7 (1.3–2.3) C</td>
<td>RR 6.0 (1.6–22.2) C</td>
</tr>
<tr>
<td>PPROM</td>
<td>OR 1.9 (1.5–2.6) B</td>
<td>OR 1.2 (1.1–1.3) B</td>
<td>OR 2.6 (1.6–4.5) C</td>
</tr>
<tr>
<td>Preterm delivery &lt;37 weeks</td>
<td>OR 1.1 (1.1–1.2) B</td>
<td>OR 1.6 (1.3–1.9) B</td>
<td>RR 1.5 (1.1–2.1) B</td>
</tr>
<tr>
<td>Very preterm delivery &lt;34 weeks</td>
<td>OR 1.5 (1.2–1.7) B</td>
<td>OR 2.7 (1.8–4.0) B</td>
<td>RR 2.4 (1.4–4.3) B</td>
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<tr>
<td>Perinatal outcome</td>
<td></td>
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<tr>
<td>Intrauterine growth restriction &lt;5th</td>
<td>No data D</td>
<td>No data D</td>
<td>No data D</td>
</tr>
<tr>
<td>Small for gestational age &lt;10th</td>
<td>NS B</td>
<td>OR 1.4 (1.2–1.6) C</td>
<td>NS C</td>
</tr>
<tr>
<td>Low birthweight &lt;2500 g</td>
<td>NS B</td>
<td>OR 1.9 (1.5–2.4) C</td>
<td>RR 2.0 (1.4–2.8) C</td>
</tr>
<tr>
<td>Very low birthweight &lt;1500 g</td>
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<td>No data D</td>
<td>D no data D</td>
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<tr>
<td>Congenital malformation</td>
<td>NS D</td>
<td>Inconclusive^{3,4} D</td>
<td>RR 1.8 (1.1–3.0) C</td>
</tr>
<tr>
<td>Low 5-min Apgar score</td>
<td>NS C</td>
<td>NS C</td>
<td>C NS C</td>
</tr>
<tr>
<td>Intrauterine fetal death</td>
<td>OR 1.9 (1.1–3.6) C</td>
<td>No data D</td>
<td>D No data D</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>OR 2.3 (1.1–4.8) C</td>
<td>NS C</td>
<td>C NS C</td>
</tr>
</tbody>
</table>

Data are reported as odds ratio (OR) or relative risk (RR) with 95% confidence interval (CI) of the best and largest studies; NS, not statistically significant; no data, no available data; PPROM, premature preterm rupture of membranes. G grade of recommendation: A, consistent level 1 studies; B, consistent level 2 or 3 studies or extrapolations from level 1 studies; C, level 4 studies or extrapolations from level 2 or 3 studies; D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

1Bhattacharya et al. (2008).
2Buchmayer et al. (2004), VPTD < 32 weeks.
3Paz et al. (1992).
4Thom et al. (1992).
5Sheiner et al. (2005), severe pre-eclampsia.
6Basson et al. (1998).
7Hammoud et al. (2007), calculated OR.
8EUROPE study, Ancel et al. (2004).
9Smith et al. (2006).
10EPIPAGE study, Moreau et al. (2005), VPTD < 32 weeks.
11Reime et al. (2008).
12Linn et al. (1983).
13Lumley (1986).
In a large population-based Swedish study of 601,883 cases, Buchmayer et al. (2004) found an increased risk of PPROM (OR 1.9, 95% CI 1.5–2.6), PTD (OR 1.1, 95% CI 1.1–1.2) and VPTD (OR 1.5, 95% CI 1.2–2.7) in women presenting with a single previous miscarriage. In other smaller studies, the risk of PPROM was not found to be increased (Thom et al., 1992; Ekwo et al., 1993; El-Bastawissi et al., 2003; Hammoud et al., 2007). An increased risk of PTD has also been reported in other studies (Pickering and Forbes, 1985; Pickering and Deeks, 1991; Lang et al., 1996; Basso et al., 1998; Smith et al., 2006; Hammoud et al., 2007; Bhattacharya et al., 2008), although not always reaching statistical significance (Schoenbaum et al., 1980; Lekea-Karanika et al., 1990; Haas et al., 1991; Thom et al., 1992; Martius et al., 1998; El-Bastawissi et al., 2003; Nguyen et al., 2004). Several large studies have also reported comparable increased risks of VPTD (Basso et al., 1998; Smith et al., 2006; Hammoud et al., 2007), whereas in smaller studies, only a slightly increased risk of

### Table II Early pregnancy events and complications as risk factors for adverse obstetric outcome in the ongoing pregnancy

<table>
<thead>
<tr>
<th>Event</th>
<th>Threatened miscarriage</th>
<th>G</th>
<th>Intrauterine haemotoma</th>
<th>G</th>
<th>CRL discrepancy</th>
<th>G</th>
<th>Vanishing twin</th>
<th>G</th>
<th>Hyperemesis gravidarum</th>
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<tr>
<td>Obstetric outcome</td>
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</tr>
<tr>
<td>Antepartum haemorrhage</td>
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<td>B</td>
<td>No data</td>
<td>D</td>
<td>No data</td>
<td>D</td>
<td>NS</td>
<td>C</td>
<td>No data</td>
<td>D</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>OR 1.4 (1.1–1.8)</td>
<td>B</td>
<td>RR 2.1 (1.5–2.9)</td>
<td>C</td>
<td>NS</td>
<td>C</td>
<td>NS</td>
<td>C</td>
<td>NS</td>
<td>C</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>OR 1.4 (1.1–1.8)</td>
<td>B</td>
<td>RR 4.0 (2.4–6.7)</td>
<td>C</td>
<td>No data</td>
<td>D</td>
<td>NS</td>
<td>C</td>
<td>NS</td>
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<tr>
<td>Placental abruption</td>
<td>OR 1.6 (1.1–2.6)</td>
<td>B</td>
<td>RR 5.6 (2.8–11.1)</td>
<td>C</td>
<td>No data</td>
<td>D</td>
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<tr>
<td>Preterm delivery &lt;37 weeks</td>
<td>OR 1.3 (1.1–1.7)</td>
<td>B</td>
<td>RR 2.3 (1.6–3.2)</td>
<td>B</td>
<td>NS</td>
<td>C</td>
<td>OR 1.6 (1.2–2.0)</td>
<td>B</td>
<td>RR 3.0 (1.9–4.3)</td>
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<td>Very preterm delivery &lt;34 weeks</td>
<td>OR 1.9 (1.6–2.2)</td>
<td>B</td>
<td>No data</td>
<td>D</td>
<td>OR 2.0 (1.1–4.0)</td>
<td>C</td>
<td>OR 3.0 (1.9–4.8)</td>
<td>B</td>
<td>No data</td>
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<tr>
<td>Intrauterine growth restriction &lt;5th</td>
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<td>D</td>
<td>No data</td>
<td>D</td>
<td>OR 2.8 (1.9–4.3)</td>
<td>C</td>
<td>No data</td>
<td>D</td>
<td>No data</td>
<td>D</td>
</tr>
<tr>
<td>Small for gestational age &lt;10th</td>
<td>NS</td>
<td>B</td>
<td>RR 2.4 (1.4–4.1)</td>
<td>B</td>
<td>OR 1.1 (1.0–1.2)</td>
<td>B</td>
<td>OR 1.6 (1.1–2.3)</td>
<td>B</td>
<td>RR 1.5 (1.0–2.2)</td>
<td>B</td>
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<td>Low birthweight &lt;2500 g</td>
<td>RR 2.3 (1.9–2.7)</td>
<td>B</td>
<td>No data</td>
<td>D</td>
<td>OR 1.8 (1.2–2.3)</td>
<td>C</td>
<td>OR 2.0 (1.5–2.6)</td>
<td>B</td>
<td>RR 2.8 (1.7–4.3)</td>
<td>B</td>
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<td>Very low birthweight &lt;1500 g</td>
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<td>No data</td>
<td>D</td>
<td>No data</td>
<td>D</td>
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<td>B</td>
<td>OR 1.4 (1.0–2.0)</td>
<td>C</td>
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<td>Congenital malformation</td>
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<td>B</td>
<td>NS</td>
<td>C</td>
<td>No data</td>
<td>D</td>
<td>NS</td>
<td>C</td>
<td>Inconclusive</td>
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<td>NS</td>
<td>C</td>
<td>RR 2.6 (1.9–3.5)</td>
<td>C</td>
<td>No data</td>
<td>D</td>
<td>No data</td>
<td>D</td>
<td>RR 5.0 (2.6–9.6)</td>
<td>C</td>
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<tr>
<td>Intrauterine fetal death</td>
<td>NS</td>
<td>B</td>
<td>NS</td>
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<td>No data</td>
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<td>NS</td>
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<tr>
<td>Perinatal death</td>
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<td>C</td>
<td>NS</td>
<td>D</td>
<td>NS</td>
<td>D</td>
<td>OR 3.7 (1.5–8.9)</td>
<td>D</td>
<td>NS</td>
<td>C</td>
</tr>
</tbody>
</table>

Data are reported as odds ratio (OR) or relative risk (RR) with 95% confidence interval (CI) of the best and largest studies; NS, not statistically significant; no data, no available data; PPROM, premature preterm rupture of membranes; CRL, crown-rump length.

G grade of recommendation: A, consistent level 1 studies; B, consistent level 2 or 3 studies or extrapolations from level 1 studies; C, level 4 studies or extrapolations from level 2 or 3 studies; D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

1Wijesiriwardana et al. (2006).
2Weiss et al. (2004).
4Spila et al. (1992).
5Hag et al. (2003).
6Smith et al. (1998), VPTD <32 weeks.
7Bukowski et al. (2007).
8Pinborg et al. (2005), calculated OR for perinatal death.
9Pinborg et al. (2007).
10Dodd et al. (2006), maternal weight gain <7 kg during pregnancy.
11Bailit et al. (2005), calculated OR.
12Gross et al. (1989).
13Bashiri et al. (1995).
These increased risks were not found in a larger study of two or more previous miscarriages. Although after two or more miscarriages, a higher risk of PE and placental abruption, PPROM, PTD, SGA, LBW and congenital anomalies after two miscarriages (Schoenbaum et al., 1992), we did not find additional information about the same risks in women with RM or about any protective effect of RM for PE (Thom et al., 1992). This might be due to the fact that studies on RM are smaller and have poor stratification and therefore possible bias in comparison to studies on two or more miscarriages.

RM is associated with an increased risk of placenta praevia (RR 6.0, 95% CI 1.6–22.2) in subsequent ongoing pregnancies (Thom et al., 1992). PPROM was associated with RM (Hammoud et al., 2007) and Thom et al. (1992) has reported on the association between RM and PTD (RR 1.5, 95% CI 1.1–2.1) and VPTD (RR 2.4, 95% CI 1.4–7.3). Similar increased odds have been reported by others (Lekea-Karania et al., 1990; Lang et al., 1996; Martius et al., 1998; Jivraj et al., 2001; Hammoud et al., 2007). The risk of PTD is increased by 25% after four or more previous miscarriages (Lekea-Karania et al., 1990; Hammoud et al., 2007).

Perinatal outcome

Only a slight increase in the risk of SGA (Pickering and Forbes, 1985; Paz et al., 1992; Thom et al., 1992; Lang et al., 1996; Basso et al., 1998) and LBW (Schoenbaum et al., 1980; Paz et al., 1992; Thom et al., 1992; Basso et al., 1998; Bhattacharya et al., 2008) has been reported by several authors in women with a single previous miscarriage. Sheiner et al. (2005) has reported no increased risk of LBW in a large population-based Israeli study of 7503 cases presenting with two or more previous miscarriages, whereas Basso et al. (1998) has observed an increased risk of SGA (OR 1.4, 95% CI 1.2–1.6) and LBW (OR 1.9, 95% CI 1.5–2.4) in a large population-based Danish study of 5268 cases presenting with two or more miscarriages.

Although it has been suggested that some congenital anomalies were associated with previous miscarriages (Paz et al., 1992) and one study has reported an increased incidence of congenital malformations after two miscarriages (Schoenbaum et al., 1980), this trend was not confirmed by a large study (Thom et al., 1992).

A single previous miscarriage is not associated with a low 5-min Apgar score, but a recent retrospective study has found an increased risk of intrauterine fetal death (OR 1.9, 95% CI 1.1–3.6) and an increased risk of neonatal death (OR 2.2, 95% CI 1.1–4.8) (Schoenbaum et al., 1980; Thom et al., 1992; Bhattacharya et al., 2008). These increased risks were not found in a larger study of two or more miscarriages (Sheiner et al., 2005).

Recurrent miscarriage

RM is conventionally defined as three or more consecutive miscarriages occurring before 20 weeks GA (Jauniaux et al., 2006). RM occurs in ~1% of fertile couples although higher incidences like 7.4% are observed (Blohm et al., 2008). The predicted risk for a subsequent miscarriage after RM ranges between 8% and 58% depending on the maternal age, the number of previous miscarriages (Brigham et al., 1999; Dawood et al., 2004) and the karyotype of previous miscarriages (Jauniaux et al., 2006). In this review, we focused on idiopathic RM because different treatments of well-established causes of RM such as thrombophilia or diabetes could have a different impact on the rate of complications in subsequent pregnancy. Only one small study fulfilled these criteria (Jivraj et al., 2001), while in all other studies, no differentiation in underlying causes of RM was made.

RM is associated with an increased risk for PE, placental abruption, placenta praevia, PPROM, PTD, SGA, LBW and congenital anomalies (Table I and Supplementary Appendix Table A3).

Obstetric outcome

Although after two or more miscarriages, a higher risk of PE and placental abruption has been reported in a large study (Sheiner et al., 2005), we did not find additional information about the same risks

Perinatal outcome

The relationship between two or more miscarriages and SGA (OR 1.4, 95% CI 1.2–1.6) found in a large population-based Danish study has already been mentioned in the previous paragraph on previous miscarriage (Basso et al., 1998). Other smaller studies have reported similar, although not statistically significant, increased risks of SGA in women with RM compared with controls (Hughes et al., 1991; Thom et al., 1992; Lang et al., 1996; Jivraj et al., 2001).

In a large case–control study, an increased risk of LBW (RR 2.0, 95% CI 1.4–2.8) has been reported in women with RM (Thom et al., 1992) and a similar trend has been reported in smaller studies (Hughes et al., 1991; Lekea-Karania and Tzoumaka-Bakoula, 1994). The finding that women presenting with RM had themselves been born with a decreased mean birthweight and an increased rate of preterm birth compared with controls suggests that the predisposition of PTD and LBW may be a genetically determined trait among women with RM (Christiansen et al., 1992).

Women with a history of RM may have a higher risk to deliver a child with congenital malformations (RR 1.8, 95% CI 1.1–3.0) than normal controls (Thom et al., 1992). No relationship has been found between RM and low 5-min Apgar score or intrauterine fetal death or perinatal death (Hughes et al., 1991; Thom et al., 1992; Jivraj et al., 2001).

Termination of pregnancy

Legal abortion is defined as a surgical or medical TOP before 24 weeks GA (Farquharson et al., 2005). Worldwide every 12–39 women/1000 women have a TOP and 31 TOPs are conducted for every 100 live births (Sedgh et al., 2007). TOP rates are lower in Western Europe than in Eastern Africa and Eastern Asia (Sedgh et al., 2007) due to better access to family planning and contraception. In developed countries, the commonly used procedure for first trimester TOP has been a vacuum aspiration. In the last decade, medical abortion with mifepristone and misoprostol has been increasingly used for pregnancies before 10 weeks gestation, whereas for second trimester TOP, the use of surgical versus medical techniques has been highly variable in different countries and regions of a same country. In a most recent large long-term safety study, no difference in the risk of miscarriage, ectopic pregnancy, PTD and LBW has
been observed between a previous TOP by medical technique or by vacuum aspiration, respectively (Virk et al., 2007).

Analysing the adverse pregnancy outcomes following a TOP is difficult because of considerable variations in the type of procedure used, the GA at the time of TOP, the number of previous TOP and the choice of an adequate control group (Atrash and Hogue, 1990). Furthermore, TOP and adverse pregnancy outcome share health behavioural pregnancy risk factors such as smoking, substance abuse, unemployment and a poor socio-economic status (Robinson et al., 2001; Raatikainen et al., 2006). Besides these confounders, the associations found between previous TOP and adverse obstetric outcome could be explained by a short interpregnancy interval, cervical damage due to cervix-dilatation, the surgical method used, GA at TOP, infection related to the procedure and tissue retention (Zhou et al., 1999, 2002). Most studies evaluating the risk of adverse pregnancy outcome in women with a history of TOP are of small size, have mixed spontaneous miscarriage and voluntary TOP and insufficiently correct for selection bias.

Despite these methodological drawbacks, it can be concluded that a history of TOP is associated with an increased risk for PPROM, PTD and VPTD. These risks depend on the number of TOP (Table I, and Supplementary Appendix Tables A4 and A5).

**Obstetric outcome**

After a history of TOP, no increased risk of PIH has been found (Eras et al., 2000). In four small studies, a low risk of PE has been found after a single TOP, similar to the low risk observed in multipara (Linn et al., 1983; Seidman et al., 1989; Stone et al., 1994; Eras et al., 2000), but a high risk of PE has been found in three small studies (Eskenazi et al., 1991; Dempsey et al., 2003; Raatikainen et al., 2006). After two or more TOP, similar risks of PE have been found (Linn et al., 1983; Eras et al., 2000; Dempsey et al., 2003; Raatikainen et al., 2006). In the EUROPE study, a history of TOP has been associated with placenta praevia (OR 2.3, 95% CI 1.3–4.0) but not with placental abruption (Ancel et al., 2004). However, in a larger case–control study, no association was found between TOP and placenta praevia, even after two or more TOP (Zhou et al., 2001).

In both the EUROPE and the EPIPAGE study, an increased risk of PPROM (OR 1.4, 95% CI 1.1–1.7 and OR 1.7, 95% CI 1.2–2.5) has been found (Ancel et al., 2004; Moreau et al., 2005, <32 weeks). The risk of PPROM is increased more (OR 1.9, 95% CI 1.3–2.9) in women presenting with two or more TOP (Linn et al., 1983). An increased risk for PTD (OR ranging 1.2–1.8) and VPTD (OR ranging 1.1–1.8) has been reported in subsequent large studies (Pickering and Forbes, 1985; Pickering and Deeks, 1991; Lang et al., 1996; Martius et al., 1998; Zhou et al., 1999; Henriet and Kaminski, 2001; El-Bastawissi et al., 2003; Ancel et al., 2004; Raatikainen et al., 2006). The rise in risk of PTD and VPTD is directly related to the number of previous TOP. In women with two or more TOP, the risk of PTD (OR ranging 1.2–2.5) and VPTD (OR ranging 1.4–2.9) is further increased (Pickering and Forbes, 1985; Lopes et al., 1991; Lang et al., 1996; Martius et al., 1998; Zhou et al., 1999; Henriet and Kaminski, 2001; El-Bastawissi et al., 2003; Ancel et al., 2004; Nguyen et al., 2004; Moreau et al., 2005; Raatikainen et al., 2006; Smith et al., 2006).

**Perinatal outcome**

In none of the studies was an association observed between one or more previous TOP and SGA, LBW, intrauterine fetal death, perinatal death, low 5-min Apgar score or congenital malformations (Schoenbaum et al., 1980; Linn et al., 1983; Pickering and Forbes, 1985; Seidman et al., 1988; Lopes et al., 1991; Mandelson et al., 1992; Lekea-Karanika and Tzoumaka-Bakoula, 1994; Lang et al., 1996; Henriet and Kaminski, 2001; Moreau et al., 2005; Raatikainen et al., 2006; Parazzini et al., 2007; Reime et al., 2008). Though two small and poor controlled studies found an association between one or more TOP and VLBW (Lumley, 1986; Reime et al., 2008).

One study has reported only a higher risk of intrauterine fetal death in women whose TOP had been complicated by an infection (Zhou and Olsen, 2003).

**Threatened miscarriage**

First trimester vaginal bleeding is the most common complication of pregnancy, occurring in 14–20% of ongoing pregnancies, whereas ~50% of these women will miscarry regardless of ultrasonographic evaluation of viability (Farrell and Owen, 1996; Everett, 1997; Weiss et al., 2004; Johns and Jauiaux, 2006; Wijesiriwardana et al., 2006). The risk of threatened miscarriage to proceed to full miscarriage depends on GA and is diminished to 2–14% after confirmation of viability (Weiss et al., 2004; Schaubberger et al., 2005; Johns and Jauiaux, 2006). An association between vaginal bleeding in the first trimester and an adverse perinatal outcome has been established for several decades (Jouppila and Koivisto, 1974; Williams et al., 1991). The majority of these older publications report on small retrospective and non-controlled studies and there are only a few state-of-the-art prospective studies available for analysis (Strobino and Pantel-Silverman, 1989; Spili, et al., 1992; Weiss et al., 2004; Johns and Jauiaux, 2006).

Vaginal bleeding during early pregnancy most often originates from the placenta. It is thought that bleeding between the chorionic membrane and the uterine wall can result in a spectrum of effects on pregnancy development and outcome. At one end, direct pressure and disruption of the placental bed can result in miscarriage. At the other end of the spectrum is placental abruption, placenta praevia, PPROM, LBW, PTD and fetal death, where there is minimal or no disruption to uteroplacental development but a chronic inflammatory reaction within the decidua and placental membranes, with weakening and eventual rupture of the membranes or resulting in myometrial activity (Johns and Jauiaux, 2006).

Threatened miscarriage in the first trimester is associated with an increased risk of APH, placental abruption, placenta praevia, PPROM, PTD, LBW and VLBW (Table II and Supplementary Appendix Table A5), and these risks are more increased in women presenting with heavy bleeding.

**Obstetric outcome**

First trimester vaginal bleeding gives a 2-fold increased risk of APH in the second and third trimester of pregnancy (Mulik et al., 2004; De Sutter et al., 2006; Wijesiriwardana et al., 2006). Women with first trimester bleeding are not at an increased risk of developing PIH and PE.
Perinatal outcome

Overall, the mean birthweight after threatened miscarriage is lower than in controls (Das et al., 1996; Weiss et al., 2004; De Sutter et al., 2006; Johns and Jauniaux, 2006). An increased risk of LBW (RR 2.3, 95% CI 1.9–2.7) and of VLBW (RR 2.2, 95% CI 1.3–3.5) was observed in a large prospective study (Williams et al., 1991) as well as in a large retrospective study (Wijesiriwardana et al., 2006). Similar increased risks of LBW and VLBW have also been reported in other small studies although not always reaching statistical significance (Funderburk et al., 1980; Hertz and Heisterberg, 1985; Strobinono and Pantel-Silverman, 1989; Sipilä et al., 1992; Lekea-Karanika and Tzoumaka-Bakoula, 1994; Das et al., 1996; Mulik et al., 2004; De Sutter et al., 2006).

Other perinatal outcomes like low 5-min Apgar score, intratuerine fetal deaths and perinatal deaths seem to be unaffected, but the risk of congenital malformation (OR 1.4, 95% CI 1.0–2.1) seems to be increased (Funderburk et al., 1980; Hertz and Heisterberg, 1985; Strobinono and Pantel-Silverman, 1989; Williams et al., 1991; Sipilä et al., 1992; Das et al., 1996; Mulik et al., 2004; De Sutter et al., 2006; Johns and Jauniaux, 2006; Wijesiriwardana et al., 2006).

Intrauterine haematoma

IUHs are crescent-shaped echolucent areas between the chorionic membrane or placenta and the myometrium (Mantoni and Pedersen, 1981; Pearstone and Baxi, 1993). In ~18–39% of the women presenting with threatened miscarriage, a subchorionic or retroplacental haematoma can be seen on ultrasound (Pedersen and Mantoni, 1990a; Johns et al., 2003). Seventy per cent of the women diagnosed with an IUH by ultrasound will experience vaginal bleeding (Ball et al., 1996; Nagy et al., 2003). An acute hemorrhage is hyperechogenic compared with the placenta, while resolving haematomas become hypoechoic within 1 week and sonoluent within 2 weeks (Nyberg et al., 1987). Persistence of a first trimester subchorionic haematoma does not affect the utero- and umbilico-placental circulation.

The risk of miscarriage is independent of vaginal bleeding, the size and the localization of the IUH; however, the risk is 2.4-fold higher when the haematoma is diagnosed before 9 weeks gestation (Pedersen and Mantoni, 1990a; Maso et al., 2005; Leite et al., 2006). An IUH during early pregnancy most often originates from the placenta. The putative mechanisms of the association of an IUH and adverse obstetric outcome are similar as described in the threatened miscarriage chapter.

An IUH is associated with an increased risk for PIH, PE, placental abruption, PTD, SGA, fetal distress and intratuerine fetal death (Table II and Supplementary Appendix Table A7).

Obstetric outcome

Women presenting with a first trimester IUH have a higher risk of PIH (RR 2.1, 95% CI 1.5–2.9), PE (RR 4.0, 95% CI 2.4–6.7), placental abruption (RR 5.6, 95% CI 2.8–11.1) and SGA (RR 2.4, 95% CI 1.4–4.1) in comparison with women without an IUH and vaginal bleeding (Nagy et al., 2003). An increased risk of placental abruption and SGA was also observed in other studies (Ball et al., 1996; Johns et al., 2003).

The risk of PPROM was not increased in women with an IUH (Ball et al., 1996; Johns et al., 2003). The risk of PTD, however, was increased (RR 2.3, 95% CI 1.6–3.2) in a prospective study comparing women with and without an IUH (Nagy et al., 2003). The increased PTD risk appeared independent of vaginal bleeding and was comparable with risks observed in other studies (Pedersen and Mantoni, 1990a; Ball et al., 1996; Mäkikallio et al., 2001; Johns et al., 2003). From older studies, it is known that there is no association between the observed incidence of premature delivery and the size of the haematoma (Pedersen and Mantoni, 1990b).

IUH specific data on LBW or VLBW were unavailable. The risks of congenital anomalies and perinatal death were not significantly increased in these women (Ball et al., 1996; Nagy et al., 2003). Fetal distress has been observed more frequently (RR 2.6, 95% CI 1.9–3.5) in these women when compared with a control group (Nagy et al., 2003), as well as intratuerine fetal death (OR 2.8, 95% CI 1.7–2.4, Ball et al., 1996).

Crown-rump length discrepancy

The classical Robinson and Fleming study on CRL is still the main reference for the assessment of GA in early pregnancy (Robinson and Fleming, 1975). Reevaluation of CRL curves based on high-resolution real-time ultrasound only demonstrated small systematic differences (Harlock et al., 1992). The predictive value of CRL measurements is
illustrated by the fact that if an embryo has developed up to 5 mm in length, subsequent loss of viability occurs in 7.2% and loss rates drop to 3.3% for embryos of 6–10 mm and to 0.5% for embryos over 10 mm (Goldstein, 1994).

A CRL discrepancy exists when the observed CRL is smaller than expected on the basis of amenorrhoea in women with a regular menstrual cycle or known date of ovulation (Reljic, 2001). A CRL discrepancy may be caused by variations in growth rate, sometimes occurring in the preimplantation period and referred to as diapause (Lopes et al., 2004). CRL discrepancy is found in certain types of aneuploidy (Kuhn et al., 1995; Schemmer et al., 1997). The discrepancy is most commonly found in first trimester fetuses with trisomy 13 and 18, and triploidy by contrast to trisomy 21 and monosomy (Kuhn et al., 1995; Goldstein et al., 1996; Bahado-Singh et al., 1997; Jauniaux et al., 1997; Falcon et al., 2005).

In ongoing euploid pregnancies, a CRL discrepancy is associated with VPTD, IUUGR, SGA and LBW, in both singleton and twin pregnancies (Table II and Supplementary Appendix Table A8).

**Obstetric outcome**

We could not find data on the association between CRL discrepancy and PIH, PE, placenta praevia, placental abruption and PPROM. A CRL discrepancy of 2–6 days is related to an increased risk of SGA (OR 1.1, 95% CI 1.0–1.2, Bukowski et al., 2007), IUUGR (OR 2.8, 95% CI 1.9–4.3) and VPTD before 32 weeks (OR 2.0, 95% CI 1.1–4.0), but it was not related to PIH nor to PTB between 33 and 36 weeks (Smith et al., 1998). Adverse pregnancy outcome has also been observed in cases presenting with a growth discrepancy of >14 days at the mid-second trimester ultrasound examination (Nakling and Backe, 2002). Furthermore in exactly dated pregnancies, conceived by assisted reproductive technology (ART), a strong association has been observed between fetal growth in first trimester and birthweight, suggesting that impairment of fetal growth starts in the first trimester (Smith, 2004; Bukowski et al., 2007; Leung et al., 2008).

A CRL discrepancy of 2–6 days smaller than expected is related to an increased risk of LBW (OR 1.7, 95% CI 1.2–2.3), but not to perinatal death (Smith et al., 1998). No data are available on the relationship between CRL discrepancy and low 5-min Apgar score, intrauterine fetal death and congenital malformation.

**Intertwin disparities in fetal size**

Intertwin disparity can be observed in both monochorionic and dichorionic twin pregnancies (Sebire et al., 1998). It has been a matter of debate whether the smaller or the larger fetus should be used to determine the GA (Kalish et al., 2003; Salomon et al., 2005). Although one study did not find an increased risk of adverse pregnancy outcomes in twins with first trimester CRL discordance (Banks et al., 2008), other studies have observed an increased risk of congenital malformation, aneuploidy, PTB, SGA, IUUGR and intertwin birthweight discordance of >20–25% when a cut-off value of >85th–95th percentile was used (Weissman et al., 1994; Kalish et al., 2003; Bartha et al., 2005; Salomon et al., 2005; Tai and Grobman, 2007). No association has been found between CRL discordance and twin-to-twin transfusion syndrome in monochorionic twin pregnancies (El Kateb et al., 2007).

**Vanishing twin**

The disappearance of gestational sacs or embryos after documented fetal heart activity in multiple pregnancies is known as the vanishing twin phenomenon (Jauniaux et al., 1988). Among pregnancies with twin sacs or embryos, ~30% will result in singletons and <10% will result in no fetuses at all (Landy and Keith, 1998; Dickey et al., 2002; Pinborg et al., 2005).

Increased levels of pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotrophin (β-hCG), potentially influencing the results of first trimester screening, have been reported in vanishing twin ART pregnancies compared with spontaneous conceived pregnancies (Chasen et al., 2006b). But, a more recently performed study did not find a difference in PAPP-A and β-hCG levels when vanishing twin pregnancies were compared with singleton ART population (Gjerris et al., 2009).

Compared with uncomplicated control ART-pregnancies with the same number of viable fetuses, there is an increase in adverse obstetrical outcome after the vanishing twin/triplet phenomenon. This might be due to early implantation crowding, resulting in an unfavourable implantation site with uteroplacental insufficiency (Depp et al., 1996), vaginal blood loss being an independent risk factor (De Sutter et al., 2006; Pinborg et al., 2007).

Although the vanishing phenomenon occurs in both spontaneously conceived and in ARTs pregnancies, the vanishing twin phenomenon described in the following studies is performed in ART-population for both cases and controls. The vanishing twin phenomenon is associated with PTB, VPTD, SGA, LBW and VLBW (Table II and Supplementary Appendix Table A9).

**Obstetric outcome**

An association with an increased risk of PE has been observed in a small study on vanishing twins (Chasen et al., 2006a) but not confirmed by a larger study (Pinborg et al., 2007). No difference is found for the risk of vaginal bleeding, placenta praevia and placental abruption, but an increased risk of SGA (OR 1.6, 95% CI 1.1–2.3) has been observed in comparison with singletons from a single gestation (Pinborg et al., 2007) and the risk increased with increasing GA at the time of vanishing. An association between vanishing twin with PTB has been observed by several authors (Dickey et al., 2002; La Sala et al., 2004; Pinborg et al., 2005; Chasen et al., 2006a; Shebl et al., 2008). An increased risk of PTB (OR 1.6, 95% CI 1.2–2.0) and VPTD before 32 weeks gestation (OR 3.0, 95% CI 1.9–4.8) has been found comparing survivors with singletons (Pinborg et al., 2005). The increased risks are almost entirely due to vanishing twins that occurred after 8 weeks gestation (Pinborg et al., 2005).

An increased risk of LBW (OR 2.0, 95% CI 1.5–2.6) and VLBW (OR 3.0, 95% CI 1.9–4.7) after a vanishing twin (Pinborg et al., 2005, 2007) has also been reported by several other studies (Dickey et al., 2002; La Sala et al., 2004; Shebl et al., 2008).

No difference has been found in the incidence of congenital malformations and perinatal death (Pinborg et al., 2005; Shebl et al., 2008). Though, in IVF/ICSI pregnancies, an increased risk of cerebral palsy in those children resulting from pregnancies, where the number of embryos transferred was higher than the number of children born, has been reported (Hvidtjærn et al., 2005). This association has not been found in vanishing twin pregnancies (Pinborg et al., 2005).
Hyperemesis gravidarum

HG is characterized by intractable nausea and vomiting leading to dehydration, electrolyte and metabolic disturbances, nutritional deficiency and weight loss. HG complicates 0.3–1.5% of all pregnancies, and in spite of extensive research during the last 4 decades, the etiology of HG remains unknown (Verberg et al., 2005). As a consequence, therapy and patient care remain empirical and symptomatic.

In women with nausea during pregnancy, the probability of miscarriage is decreased (OR 0.3, 95% CI 0.2–0.3) and this is directly linked with the severity of symptoms (Maconoche et al., 2007). Also adverse obstetric outcome is linked with the severity of the symptoms. The adverse obstetric outcome is mostly limited to women with a poor maternal weight gain during pregnancy (Dodds et al., 2006). This suggests that deficient malnutrition and the lack of vitamins and oligo-elements could play a role in these associations.

Severe hyperemesis is associated with PTD, SGA, LBW, low 5-min Apgar score and possibly also with fetal congenital anomalies (Table II and Supplementary Appendix Table A10).

Obstetric outcome

There are many observations about an increased incidence of female neonates (53–66%) in pregnancies complicated by HG (Schiff et al., 2004).

Women with HG do not present with a higher risk to develop PIH and PE (Bashiri et al., 1995; Dodds et al., 2006). Infants of mothers with HG have a higher PTD risk, as well as a higher risk for LBW and VLBW, and these neonates are more likely to be SGA (Bashiri et al., 1995; Bailit, 2005; Dodds et al., 2006). The increased risks are probably due to the low pregnancy weight gain (<7 kg during pregnancy) because it has been demonstrated that women with HG and >7 kg weight gain during pregnancy do not have an increased risk of PTD, LBW, VLBW and SGA (Gross et al., 1989; Vilming and Nesheim, 2000; Dodds et al., 2006). Other studies, evaluating the effect of only low maternal weight gain during pregnancy on pregnancy outcome, have also found an increased risk of PTD, LBW and VLBW (Ehrenberg et al., 2003; DeVader et al., 2007; Tsukamoto et al., 2007). In a large retrospective study on women with HG and a low weight gain of <7 kg, an increased risk of PTD (RR 3.0, 95% CI 1.9–4.3), SGA (RR 1.5, 95% CI 1.0–2.2), LBW (RR 2.8, 95% CI 1.7–4.3) and low 5-min Apgar score (RR 5.0, 95% CI 2.6–9.6) has been found compared with normal pregnancies (Dodds et al., 2006).

There are only a few data on the increased risk of congenital anomalies in HG women (Gross et al., 1989; Hod et al., 1994; Hallack et al., 1996; Kawamura et al., 2008). There is an increased risk of anomalies of the central nervous system and skeletal malformations most likely due to nutritional deficiencies in oligo-elements and vitamins such as folic acid and vitamin K. No difference has been found in the incidence of intrauterine fetal death and perinatal death (Bashiri et al., 1995; Hallack et al., 1996; Tsang et al., 1996; Bailit, 2005; Dodds et al., 2006).

Pregnancy with an IUD

IUDs are widely used as contraceptives. A cumulative pregnancy rate of <2% for a copper IUD and ~1% for a levonorgestrel-releasing IUD has been reported (Thonneau et al., 2001). Dislocation of the IUD is frequently observed in pregnant women with an IUD (Inal et al., 2005).

Pregnancies developing with an IUD in situ are associated with an increased risk of early and late miscarriage and PTD.

Obstetric outcome

A few studies have found that ongoing pregnancies with an IUD left in situ have a 2-fold increase in the risk of early and late miscarriage (50–57%) and a 4-fold increase in risk of PTD (17–22%), compared with controls in which the IUD is removed in first trimester (Tatum et al., 1976; Koetsawang et al., 1977). It is advised to remove the IUD with visible strings, as following removal of the IUD, the chance of miscarriage (20–25%) and PTD (4–6%) is decreased (Tatum et al., 1976; Koetsawang et al., 1977). If the strings of the IUD are not visible, it can be considered to remove the IUD under ultrasound guidance or by hysteroscopy (Kirkinnen et al., 1992; Schiesser et al., 2004). These are observational studies and there are no RCTs comparing obstetric outcome in IUD in situ or after removal of an IUD and controls.

Intrauterine exposure to copper is not associated with any known teratogenic effect (Tatum et al., 1976; Barash et al., 1990). Teratogenic effects of a levonorgestrel-releasing IUD have not been reported.

Conclusions

In this comprehensive review, we describe the impact of various specific first trimester events and complications for adverse effects on pregnancy outcome in second or third trimester of pregnancy. A few of these associations are based on large good-controlled population-based or prospective studies. Though many studies describing the impact of a single first trimester complication are small, retrospective series, have poor stratification bias and poor matching of cases and controls. Many of the controlled studies did not make adjustments for all known relevant confounders for adverse obstetric outcome, such as age, ART, economical status, education level, ethnicity, length, marital status, parity, previous obstetric outcome, prolonged infertility smoking and maternal weight or did not stratify for other first trimester complications. More large controlled studies, using local National Birth Registries, are needed to confirm our findings. In particular, larger studies concerning the risk of adverse late pregnancy outcome in women presenting with idiopathic RM, IUH and CRL discrepancy are needed.

Data from our literature review indicate a strong association between specific early pregnancy events and subsequent late obstetric complications in the subsequent or ongoing pregnancy. In particular, the risk of PTD and VPTD is increased after any of these first trimester complications. In all specific early pregnancy complications, the increased risks of late obstetric complications are related to the severity and/or to the recurrence of the first trimester complication. Though some of the found associations are small (between OR 1.0 and 2.0) and thus the clinical relevance of these associations could be questionable.

Clinically relevant associations (grade of recommendation A, B or C) of adverse obstetric and perinatal outcome in the subsequent pregnancy with an OR > 2.0 after complications in a previous pregnancy are the risk of perinatal death after a single previous miscarriage, the
risk of VPTD after two or more miscarriages, the risk of placenta praevia, PROM, VPTD and LBW after RM and the risk of VPTD after two or more TOP. Clinically relevant associations (grade of recommendation A, B or C) of adverse obstetric and perinatal outcome in the ongoing pregnancy with an OR > 2.0 after complications in the index pregnancy are the risk of LBW and VLBW after a threatened miscarriage, the risk of PIH, PE, placental abruption, PTD, SGA and low 5-min Apgar score after detection of an IUH, the risk of VPTD and IUGR after a CRL discrepancy, the risk of VPTD, LBW and VLBW after a vanishing twin phenomenon and the risk of PTD, LBW and low 5-min Apgar score in a pregnancy complicated by severe HG. The identification of these high risk groups should enable better management protocols and new therapeutic protocols to improve neonatal outcome.

**Supplementary data**

Supplementary data are available at http://molehr.oxfordjournals.org/.

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Predicting adverse obstetric outcome


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