Human Reproduction Update, Vol.15, No.4 pp. 409–421, 2009
Advanced Access publication on March 7, 2009 doi:10.1093/humupd/dmp009

human reproduction update

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

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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 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 (recurrent) 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 placental 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).

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

	Previous miscarriage				Recurrent miscarriage		Termination of pregnancy			
	One	G	Two or more	G	Three or more	G	One	G	Two or more	G
Obstetric outcome										
Pregnancy-induced hypertension	NS	D	NS	D	No data	D	NS	D	No data	D
Pre-eclampsia	OR 3.3 (2.6–4.6)[1]	D	OR 1.5 (1.3–1.8)[5]	C	NS	C	NS	C	NS	C
Placental abruption	NS	C	OR 1.5 (1.1–1.7)[5]	C	NS	C	NS	D	NS	D
Placenta praevia	NS	C	OR 1.7 (1.3–2.3)[5]	C	RR 6.0 (1.6–22.2)[4]	C	NS	C	NS	C
PPROM	OR 1.9 (1.5–2.6)[2]	B	OR 1.2 (1.1–1.3)[5]	B	OR 2.6 (1.6–4.5)[7]	C	OR 1.4 (1.1–1.7)[8]	B	OR 1.9 (1.3–2.9)[12]	C
Preterm delivery <37 weeks	OR 1.1 (1.1–1.2)[2]	B	OR 1.6 (1.3–1.9)[2]	B	RR 1.5 (1.1–2.1)[4]	B	OR 1.2 (1.1–1.3)[9]	B	OR 1.9 (1.4–2.5)[9]	B
Very preterm delivery <34 weeks	OR 1.5 (1.2–1.7)[2]	B	OR 2.7 (1.8–4.0)[2]	B	RR 2.4 (1.4–4.3)[4]	B	OR 1.5 (1.1–2.0)[10]	B	OR 2.6 (1.1–5.9)[10]	B
Perinatal outcome										
Intrauterine growth restriction <5th	No data	D	No data	D	No data	D	No data	D	No data	D
Small for gestational age <10th	NS	B	OR 1.4 (1.2–1.6)[6]	C	NS	C	NS	B	NS	B
Low birthweight <2500 g	NS	B	OR 1.9 (1.5–2.4)[6]	C	RR 2.0 (1.4–2.8)[4]	C	NS	B	NS	D
Very low birthweight <1500 g	No data	D	No data	D	no data	D	OR 2.7 (1.1–7.1)[11]	D	OR 3.6 (2.3–5.5)[13]	D
Congenital malformation	NS	D	Inconclusive[3,4]	D	RR 1.8 (1.1–3.0)[4]	C	NS	B	NS	D
Low 5-min Apgar score	NS	C	NS	C	NS	C	NS	C	NS	C
Intrauterine fetal death	OR 1.9 (1.1–3.6)[1]	C	No data	D	No data	D	NS	B	NS	C
Perinatal death	OR 2.3 (1.1–4.8)[1]	C	NS	C	NS	D	NS	B	NS	C

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.
[1]Bhattacharya *et al.* (2008).
[2]Buchmayer *et al.* (2004), VPTD < 32 weeks.
[3]Paz *et al.* (1992).
[4]Thom *et al.* (1992).
[5]Sheiner *et al.* (2005), severe pre-eclampsia.
[6]Basso *et al.* (1998).
[7]Hammoud *et al.* (2007), calculated OR.
[8]EUROPE study, Ancel *et al.* (2004).
[9]Smith *et al.* (2006).
[10]EPIPAGE study, Moreau *et al.* (2005), VPTD < 32 weeks.
[11]Reime *et al.* (2008).
[12]Linn *et al.* (1983).
[13]Lumley (1986).

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

	Threatened miscarriage	G	Intrauterine haematoma	G	CRL discrepancy	G	Vanishing twin	G	Hyperemesis gravidarum	G
Obstetric outcome										
Antepartum haemorrhage	OR 1.8 (1.7–2.0)[1]	B	No data	D	No data	D	NS	C	No data	D
Pregnancy-induced hypertension	OR 1.4 (1.1–1.8)[2]	B	RR 2.1 (1.5–2.9)[5]	C	NS	C	NS	C	NS	C
Pre-eclampsia	OR 1.4 (1.1–1.8)[2]	B	RR 4.0 (2.4–6.7)[5]	C	No data	D	NS	C	NS	D
Placental abruption	OR 1.6 (1.1–2.6)[2]	B	RR 5.6 (2.8–11.1)[5]	C	No data	D	NS	C	No data	D
Placenta praevia	NS	B	No data	D	No data	D	NS	C	No data	D
PPROM	NS	B	NS	D	no data	D	no data	D	No data	D
Preterm delivery <37 weeks	OR 1.3 (1.1–1.7)[2]	B	RR 2.3 (1.6–3.2)[5]	B	NS	C	OR 1.6 (1.2–2.0)[8]	B	RR 3.0 (1.9–4.3)[10]	C
Very preterm delivery <34 weeks	OR 1.9 (1.6–2.2)[1]	B	No data	D	OR 2.0 (1.1–4.0)[6]	C	OR 3.0 (1.9–4.8)[8]	B	No data	D
Perinatal outcome										
Intrauterine growth restriction <5th	No data	D	No data	D	OR 2.8 (1.9–4.3)[6]	C	No data	D	No data	D
Small for gestational age <10th	NS	B	RR 2.4 (1.4–4.1)[5]	B	OR 1.1 (1.0–1.2)[7]	B	OR 1.6 (1.1–2.3)[9]	B	RR 1.5 (1.0–2.2)[10]	B
Low birthweight <2500 g	RR 2.3 (1.9–2.7)[3]	B	No data	D	OR 1.8 (1.2–2.3)[6]	C	OR 2.0 (1.5–2.6)[8]	B	RR 2.8 (1.7–4.3)[10]	B
Very low birthweight <1500 g	RR 2.2 (1.3–3.5)[3]	B	No data	D	No data	D	OR 3.0 (1.9–4.7)[8]	B	OR 1.4 (1.0–2.0)[11]	C
Congenital malformation	OR 1.4 (1.0–2.1)[4]	B	NS	C	No data	D	NS	C	Inconclusive[12,13]	D
Low 5-min Apgar score	NS	C	RR 2.6 (1.9–3.5)[5]	C	No data	D	No data	D	RR 5.0 (2.6–9.6)[10]	C
Intrauterine fetal death	NS	B	NS	D	No data	D	No data	D	NS	C
Perinatal death	NS	C	NS	D	NS	C	OR 3.7 (1.5–8.9)[8]	D	NS	C

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.
[1]Wijesiriwardana *et al.* (2006).
[2]Weiss *et al.* (2004).
[3]Williams *et al.* (1991).
[4]Sipilä *et al.* (1992).
[5]Nagy *et al.* (2003).
[6]Smith *et al.* (1998), VPTD <32 weeks.
[7]Bukowski *et al.* (2007).
[8]Pinborg *et al.* (2005), calculated OR for perinatal death.
[9]Pinborg *et al.* (2007).
[10]Dodds *et al.* (2006), maternal weight gain <7 kg during pregnancy.
[11]Bailit *et al.* (2005), calculated OR.
[12]Gross *et al.* (1989).
[13]Bashiri *et al.* (1995).

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

VPTD was reported (Thom *et al*., 1992; Martius *et al*., 1998; El-Bastawissi *et al*., 2003; Bhattacharya *et al*., 2008). In all studies, the risk of PPROM (OR 1.2, 95% CI 1.1–1.3), PTD (OR 1.6, 95% CI 1.3–1.9) and VPTD (OR 2.7, 95% CI 1.8–4.0) is increased more in women presenting with two or more miscarriages when compared with women with only a single previous miscarriage (Buchmayer *et al*., 2004; Sheiner *et al*., 2005).

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 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-Karanika *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-Karanika *et al*., 1990; Hammoud *et al*., 2007).

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-Karanika 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; Nguyen et al., 2004; Moreau et al., 2005; Smith et al., 2006; Reime et al., 2008) and small studies (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 Jauniaux, 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; Schauberger et al., 2005; Johns and Jauniaux, 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; Sipilä et al., 1992; Weiss et al., 2004; Johns and Jauniaux, 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 Jauniaux, 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 A6), 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

(Johns *et al*., 2003; Weiss *et al*., 2004; Johns and Jauniaux, 2006; Wijesiriwardana *et al*., 2006).

In large prospective cohort study, threatened miscarriage was found to be a risk factor for placental abruption, after a light bleeding (OR 1.6, 95% CI 1.1–2.6) as well as after a heavy bleeding (OR 3.6, 95% CI 1.6–7.9) (Weiss *et al*., 2004). A comparable increased risk of placental abruption (OR 2.8, 95% CI 2.0–3.7) was also observed in a large retrospective case–control study (Mulik *et al*., 2004) and in another study (Wijesiriwardana *et al*., 2006). The risk of placenta praevia in threatened miscarriage is increased (OR 1.8, 95% CI 1.1–2.9) in a large retrospective study (Wijesiriwardana *et al*., 2006). In a subgroup with heavy bleeding of a prospective study, the same risk is increased (OR 2.5, 95% CI 0.9–6.9), however not significantly (Weiss *et al*., 2004).

Women presenting with heavy bleeding are at higher risk of SGA (OR 2.6, 95% CI 1.2–5.6) (Weiss *et al*., 2004), whereas women with light bleeding are not at increased risk (Sipilä *et al*., 1992; Johns *et al*., 2003; Weiss *et al*., 2004; De Sutter *et al*., 2006). In almost all studies, a 1.9–3.7-fold increased risk of PPROM is observed (Hertz and Heisterberg, 1985; Weiss *et al*., 2004; Yang *et al*., 2004; De Sutter *et al*., 2006; Johns and Jauniaux, 2006) except in one (Wijesiriwardana *et al*., 2006). An increased risk of PTD (RR ranging 1.3–3.1) and VPTD (RR ranging 1.6–5.3) is found in all studies after threatened miscarriage, in both normal and IVF pregnancies (Funderburk *et al*., 1980; Hertz and Heisterberg, 1985; Strobino and Pantel-Silverman, 1989; Williams *et al*., 1991; Sipilä *et al*., 1992; Das *et al*., 1996; Johns *et al*., 2003; Mulik *et al*., 2004; Nguyen *et al*., 2004; Weiss *et al*., 2004; Yang *et al*., 2004; De Sutter *et al*., 2006; Johns and Jauniaux, 2006; Wijesiriwardana *et al*., 2006). The risk of PTD is increased more (OR 3.0, 95% CI 1.9–4.5) after heavy first trimester bleeding (Strobino and Pantel-Silverman, 1989; Nguyen *et al*., 2004; Weiss *et al*., 2004).

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; Strobino 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, intrauterine 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; Strobino 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; Pearlstone 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 haemorrhage is hyperechogenic to isoechogenic compared with the placenta, while resolving haematomas become hypoechogenic within 1 week and sonolucent 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 intrauterine 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 intrauterine 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 (Hadlock *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 (Reljič, 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, IUGR, 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), IUGR (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 PTD 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, PTD, SGA, IUGR 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 PTD, 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 PTD 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 PTD (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 (Hvidtjørn *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 aetiology 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 (Maconochie *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 levonorgestel-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 (Kirkinen *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, PPROM, 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://humupd.oxfordjournals.org/.

Acknowledgements

We thank Prof. G.J. Bonsel, PhD, Institute of Health Policy and Management (iBMG), Erasmus University Medical Center, The Netherlands, for his critical reading of the manuscript and his advice.

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Submitted on October 7, 2008; resubmitted on January 5, 2009; accepted on February 7, 2009