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Review article

Final outcome of a second trimester low-positioned placenta: A systematic review and meta-analysis

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ABSTRACT

Low-positioned placentas which are located in the lower uterine segment (LUS), either a low-lying placenta or a placenta previa, are associated with increased obstetric risks. However, most second trimester low-positioned placentas resolve during pregnancy and have a higher position in the third trimester, without posing any risks.

We performed a systematic review and meta-analysis to evaluate the proportion of second trimester low-positioned placentas that have a position towards the fundus in the third trimester. Our aim was to find a cut-off value that included all women in whom the placenta will remain low in the third trimester, thus who are at increased risk of obstetric complications. Subsequently, we assessed whether an anterior or posterior placental location influenced this proportion.

We searched MEDLINE and EMBASE and clinicaltrials.gov up to April 2019 for studies on the sonographic follow-up of second trimester low-positioned placentas, with a distance between the placenta and the internal os of the cervix of 20 mm or less at a gestational age of above 15 week and a follow up after 28 weeks. Studies were scored on methodological quality using the Newcastle-Ottowa Scale (NOS). A meta-analysis was conducted to summarize the proportion of second trimester low-positioned placentas with a position towards the fundus in the third trimester. We calculated the proportion at different cut-off values of the distance from the placental edge to the internal os of the cervix (0 mm, 10 mm and 20 mm). Also, anteriorly and posteriorly located placentas and women with and without a prior cesarean delivery were compared.

We included 11 eligible studies which reported on 3586 women with a low-positioned placenta in the second trimester. Proportions of placentas with a position towards the fundus in the third trimester ranged between 0.63 and 1.0. Pooled proportions were 0.90 (95% CI 0.87-0.93) for IOD <10 mm and 0.80 (95% CI 0.74-0.85) for IOD < 0 mm. Due to heterogeneity between studies, the subgroup of <20 mm could not be pooled. Overall, anteriorly located placentas more often had a position towards the fundus in the third trimester, but studies did report conflicting results. Prior cesarean section had no influence except for an IOD of <0 mm, in which women without a prior cesarean delivery more often had a placenta towards the fundus.

The majority of second trimester low-positioned placentas will be located towards the fundus at the time of follow-up. However, we could not determine a cut-off value for anterior and posterior placentas that included all women at high risk. The cut-off value, placental side and prior cesarean section should be assessed in a large prospective observational study.

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Contents

Introduction

Low-positioned placentas which are located in the lower uterine segment (LUS), either a low-lying placenta or a placenta previa, are associated with increased obstetric risks, due to blood loss in the third trimester and hemorrhage during delivery [1–3]. Therefore, for women with a low-positioned placenta in the second trimester, a follow-up ultrasound in the third trimester could be recommended. However, a phenomenon generally called 'placental migration', in which a low-lying placenta or placenta previa resolves as pregnancy continues, occurs in more than 90% of cases. Hereby, the incidence of a low-positioned placenta decreases from 5% in the second trimester to 0.3-0.9% in the third trimester [4]. Thus, a group of women will have a placenta located outside the LUS in the third trimester, without any risks, but a high-risk group will have a placenta located inside the LUS in the third trimester. Identifying these high- and low-risk groups in the second trimester could lower the burden and costs of follow-up ultrasound visits, prevent unnecessary lifestyle limitations and decrease anxiety in women in the low-risk group [5,6].

Current guidelines use different cut-off values for the distance between the internal os of the cervix and the placental edge (internal os distance, IOD) that requires follow-up ultrasound in the third trimester. The Dutch Association of Obstetrics and Gynaecology (NVOG) guideline advises to perform a follow-up scan in the third trimester, if the placenta is located in the LUS at the second trimester anomaly scan, without mentioning a cut-off value [1]. The British Royal College of Obstetricians and Gynaecologists (RCOG) recommend a evaluation at 32 weeks of gestation if the placenta is lying less than 20 mm away from the internal os. The Society of Obstetrics and Gynaecology of Canada (SOGC) guideline recommends follow-up when the placenta reaches or overlaps the internal cervical os at the second trimester anomaly scan [7,8]. The American College of Obstetrics and Gynaecology (ACOG) and the Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG) refer to the RCOG [7]. None of the guidelines distinguish between anteriorly and posteriorly located placentas or women with or without a prior cesarean delivery. In this systematic review and meta-analysis, we aimed to define which second trimester low-positioned placentas will remain low-positioned in the third trimester and therefore have an increased risk of obstetric complications, warranting follow-up ultrasound in the third trimester. Furthermore, we aimed to determine if there is a difference in migration between anteriorly and posteriorly located placentas and in women with and without a prior cesarean delivery.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. The research protocol was published in Prospero (systematic review record CRD42016035392). This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Since this is a review, there was no direct patient- and public involvement in our study.

Eligibility criteria, information sources, search strategy

Publications on the follow-up of a second trimester low-positioned placenta were considered eligible for inclusion. A medical librarian (J.L.) performed a comprehensive search in OVID MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations), OVID EMBASE and clinicaltrials.gov from inception to April 2019 10th. The broad search strategy consisted of controlled terms (i.e. MesH-terms) and text words for placenta previa and ultrasound, screening, migration, distance, dynamic etc., combined with a search filter to find original studies or systematic reviews. Language or date restrictions were not applied. We cross-checked reference lists and citing papers of identified relevant publications via Web of Science. The complete search strategies are shown in Appendix A1. The records retrieved were imported and deduplicated in ENDNOTE X7.5.

Study selection

Studies reporting on placental location by ultrasound in both the second trimester and follow-up in the third trimester in case of

a low-positioned placenta were eligible for inclusion. We included articles in which the placental location had been evaluated between 15 and 28 weeks of gestation for the first time and after 28 weeks of gestation onwards for the second time. We included articles using the following definitions of a low-positioned placenta: 1) a placenta previa in which the placenta completely covers the internal ostium, and 2) a low-lying placenta in which the edge of the placenta is near to (<20 mm) but not overlying the os. [4] All placentas had to be evaluated with transabdominal and/or transvaginal ultrasound. Studies that did not define a second trimester low-positioned placenta using an IOD in millimeters were excluded. Studies in which placental location was confirmed only during cesarean delivery, without ultrasound, were excluded. We considered randomized controlled trials, prospective and retrospective cohort studies, case-control studies and case series of >10 cases for inclusion. Case reports, editorials, comments and (systematic) reviews were excluded.

Data extraction

Studies were included in a two-stage process. First, in- and exclusion criteria were applied by two authors (C.J., L.R.), who independently scanned the titles and abstracts. Final inclusions were made after full-text screening by the two reviewers. Discrepancies in inclusion were discussed until mutual agreement was achieved and, if necessary, a third reviewer (E.P.) was consulted. Authors were approached if the full-text article was not available. Articles were excluded if full-text could not be received. After selecting eligible studies, data extraction was completed by one reviewer (C.J.) using a predesigned data extraction form. The clinical study characteristics which were extracted included author, country, publication year, study design, inclusion period, type of ultrasound being transabdominal sonography (TAS) or transvaginal sonography (TVS), definition/cut-off used for low-positioned placenta in millimeters (mm), gestational weeks (GA) at first ultrasound, GA at follow-up, number of women with low-positioned placenta in the second trimester. We categorized all articles in three groups based on the cut-off value used for definition of low-lying placenta: IOD of 20 mm, IOD of 10 mm or 0 mm/overlapping the internal os of the cervix. The number of women with a placenta towards the fundus in the third trimester was extracted for the whole group and subsequently for anteriorly and posteriorly located placentas if this information was provided. Also, information concerning the influence of a previous cesarean section was extracted.

Assessment of risk of bias

The quality of the included studies and the risk of bias was independently assessed by the two reviewers (C.J., L.R.). The included studies were scored on methodological quality using predesigned characteristics based on the Newcastle-Ottawa Scale (NOS). The NOS serves to carefully assess the quality of analytical studies such as cohort studies and case-control studies and is recommended by the Cochrane collaboration of assessing non-randomized studies. [10] Separate NOS scales were used for cohort studies and case-control studies, which could be included in this review. All studies were scored on *selection, comparability* and *outcome* for which respectively 4 stars, 2 stars and 3 stars could be given. The NOS checklist is included in Appendix A2. [11]

Data synthesis

From all included studies, we obtained the proportion of women with a low-positioned placenta in the second trimester and a position towards the fundus (i.e. any upward migration) in the third trimester. Study results were grouped by definition of low-positioned placenta in the second trimester (IOD cut-off values of 20 mm, 10 mm and 0 mm/overlapping the internal os of the cervix) and position of the placenta in the third trimester, as defined by the authors of the original studies (>20 mm, >10 mm or >0 mm from the internal os). We created a forest plot for visualization of the results. When the confidence intervals of the studies within one group overlapped each other, we deemed it appropriate to pool the results with a random effects model using the DerSimonian Liard method. Within the original studies, we compared proportions of migration between anteriorly and posteriorly located placentas, or between women with and without a previous cesarean section, with a Chi-square test.

All analyses were done using R for Windows 3.5.1. [12] For meta-analyses and plots we used the "metafor" package [13]. A p-value of < 0.05 was considered statistically significant.

Results

Study selection

Of the 1184 unique publications identified, 1138 were excluded after reading title and abstract, either because they were not eligible (n = 1130) and eight articles were excluded because they were guidelines (n = 4), a case audit (n = 1), case reports (n = 2) and a letter to the editor (n = 1). Of the remaining 46 articles, 35 were excluded after assessing the full-text. Five articles did not document the desired outcome, [6,14–17] 11 articles described the first evaluation moment either before GA of 15 weeks and/or after GA of 28 weeks [3,18–28]. nine articles did not mention the IOD cut-off value [29–37], and two articles used a cut-off value of 30 mm without reporting separate results for the group with IOD < 20 mm. [38,39]. From eight articles the full-text was not available and the authors could not be reached [40–47], leaving eleven studies for final analysis (Fig. 1]). [5,48–56]

Study characteristics

Table 1 gives an overview of the characteristics of the included studies. Three studies were retrospective cohort studies and eight were prospective cohort studies. Six studies used both TAS and TVS, three studies used TVS and two studies used TAS. Of the included studies, three used a cut-off value of 0 mm, only one study used a cut-off value of 10 mm and seven used 20 mm as a cut-off value. A total number of 3586 women with a low-positioned placenta in the second trimester were included. Four studies reported the placental side in the second and the third trimester.

Risk of bias of included studies

All of the studies scored six stars according to the Newcastle Ottowa Scale (NOS), three out of four stars for the selection criteria and three out of three stars for the outcome criteria, reflecting good study quality. We could not include comparability in our quality assessment scale since none of the studies used a control group nor controlled for any factors. The table with the quality assessment scale is shown in Appendix A3.

Synthesis of results

Proportion of placentas with a position towards the fundus in the third trimester

The proportion of placentas with a position towards the fundus in the third trimester are shown in Table 2 and graphically in Fig. 2. The data of second trimester placentas with a cut-off of < 20 mm could not be pooled but showed proportions between 0.63 and 1.0

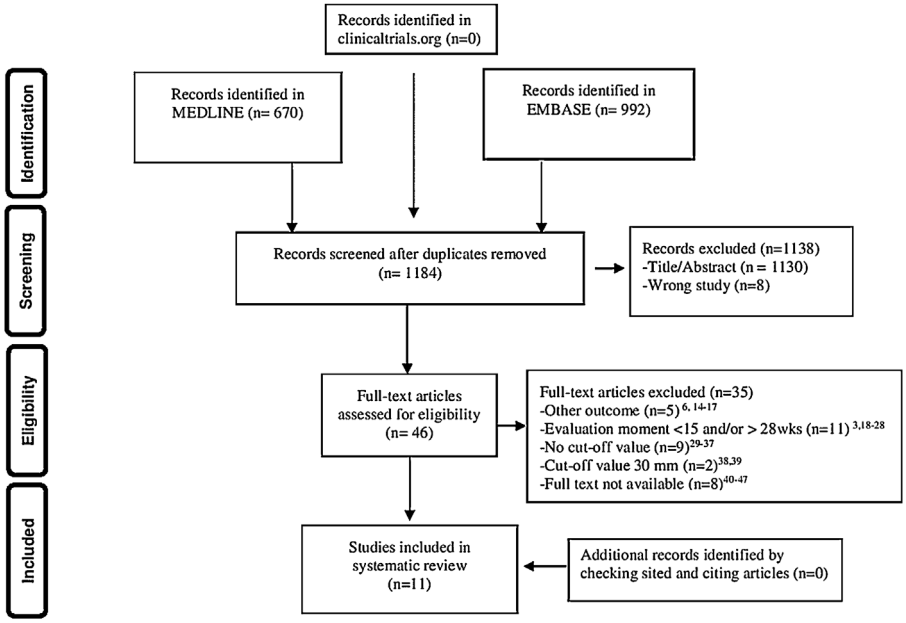

Fig. 1. Flowchart summarizing study selection of papers on the sonographic placental location in the second and third trimester.

in the original studies. The pooled data of placentas with a cut-off of < 10 mm showed a proportion of 0.90 (95% CI 0.87-0.93) and a cut-off of < 0 mm showed a proportion of 0.80 (95% CI 0.74-0.85).

Placental side

In the articles that reported on the placental side, posteriorly located placentas (n = 1076) were more common in the second trimester than anteriorly located placentas (n = 519). Using a cut-off value of 0 mm, no significant difference between the location towards the fundus of anteriorly and posteriorly located placentas in the third trimester was observed (anterior 18/27 (0.67) vs posterior 32/40 (0.80), p-value 0.2). [38,50] The three studies using a cut-off value of 20 mm did show significant differences between anteriorly and posteriorly located placentas. In a cohort of 183 patients, significantly more posteriorly located placentas were found to have a distance of > 20 mm in the third trimester, 48/61 (0.79) anteriorly located placentas versus 112/122 (0.92) posteriorly located placentas, p-value 0.01. The two other cohorts however, showed a significant difference favoring the anterior side. In a cohort 98 patients, more anteriorly located placentas had a distance of > 20 mm in the third trimester; 28/29 (0.97) anteriorly located placentas versus 52/69 (0.75) posteriorly located placentas, p-value 0.01. [48]. The biggest cohort of 1254 women showed more anteriorly located placentas to be outside the LUS in the third trimester, anterior 371/375 (0.99) versus posterior 764/812 (0.94), p-value <0.01. [56].

Table 1
study characteristics.

Author, country, year	Study type	Inclusion period	US	Cut-off value	First US GA wks	Follow-up US GA wks	Women with low-positioned placenta in 2nd trimester (N)
Cho [48], Korea, 2006	Prosp. cohort	2004-2005	TVS	<20 mm	20-27	32-37	98
Copland [5], New-Zealand, 2012	Retros. cohort	2005-2008	TAS	<20 mm	18-20	32-34	350
Durst, USA [56], 2018	Retros. Cohort	2010-2015	TVS	<20 mm	18-24	28-32-36	1254
Feng [57], China, 2017	Prosp. cohort	2014-2015	TAS/ TVS	<20 mm	20-26	37	183
Heller [49], USA, 2013	Retros. cohort	2007-2011	TAS/ TVS	<20 mm	16-24	36	1240
Lal [50], USA, 2011	Prosp. cohort	2007-2011	TVS	0 mm	An. scan	Every 4-6 wks	67
Lauria [51], USA,1996	Prosp. cohort	1995-1996	TAS/ TVS	0 mm	15-24	Delivery	36
Naji [52], UK, 2012	Prosp. cohort	2010-2011	TAS	<20 mm	20	32	60
Quant [53], USA, 2014	Prosp. cohort	2012	TAS/ TVS	<10 mm	18-24	3rd trim.	41
Robinson [54], New-Zealand, 2012	Prosp. cohort	2007–2008	TAS/ TVS	<20 mm	An. scan	>28	205
Taipale [55], Finland, 1998	Prosp. cohort	1995-1996	TAS/ TVS	0 mm	18-23	26-30	52

GA Gestational ageAn. ScanAnomaly scan (GA 18–24 wks).
TASTrans abdominal sonographyUS Ultrasound.
TVS Trans vaginal sonography MmMillimeters.

Table 2
Anteriorly and posteriorly located placentas with a position towards the fundus in the third trimester.

Cut-off value	Author	Women with low-positioned placenta in 2nd trimester	Location towards the fundus in 3rd trimester (% of total)	Women with anteriorly located low-positioned placenta in 2nd trimester (% of total)	Location towards the fundus of anterior placentas in 3rd trimester (% of anterior)	Women with posteriorly located low-positioned placenta in 2nd trimester (% of total)	Location towards the fundus of posterior placentas in 3rd trimester (% of posterior)
< 20 mm	Cho	98	80/98 (82)	29 (30)	28/29 (93)	69 (70) *	52/69 (75)*
	Copland	350	317/350 (91)				
	Durst	1254	1184/1254 (94)	375 (30)***	371 (99)	812 (65)***	764 (94)
	Feng	183	160/183 (87)	61 (33)	48/61 (79)	122 (67)**	112/122 (92)**
	Heller	1240	1220/1240 (98)				
	Naji	60	38/60 (63)	27 (45)	not reported	33 (55)	not reported
	Robinson	205	204/205 (99.5)				
<10 mm	Quant	41	37/41 (90)				
< 0 mm	Lal	67	55/67 (82)	27 (40)	18/27 (67)	40 (60)	32/40 (80)
	Lauria	36	31/36 (86)				
	Taipale	52	42/52(81)				

* significant difference between anteriorly and posteriorly located placentas favoring anterior.
** significant difference between anteriorly and posteriorly located placentas, favoring posterior.
*** location not known of all women.

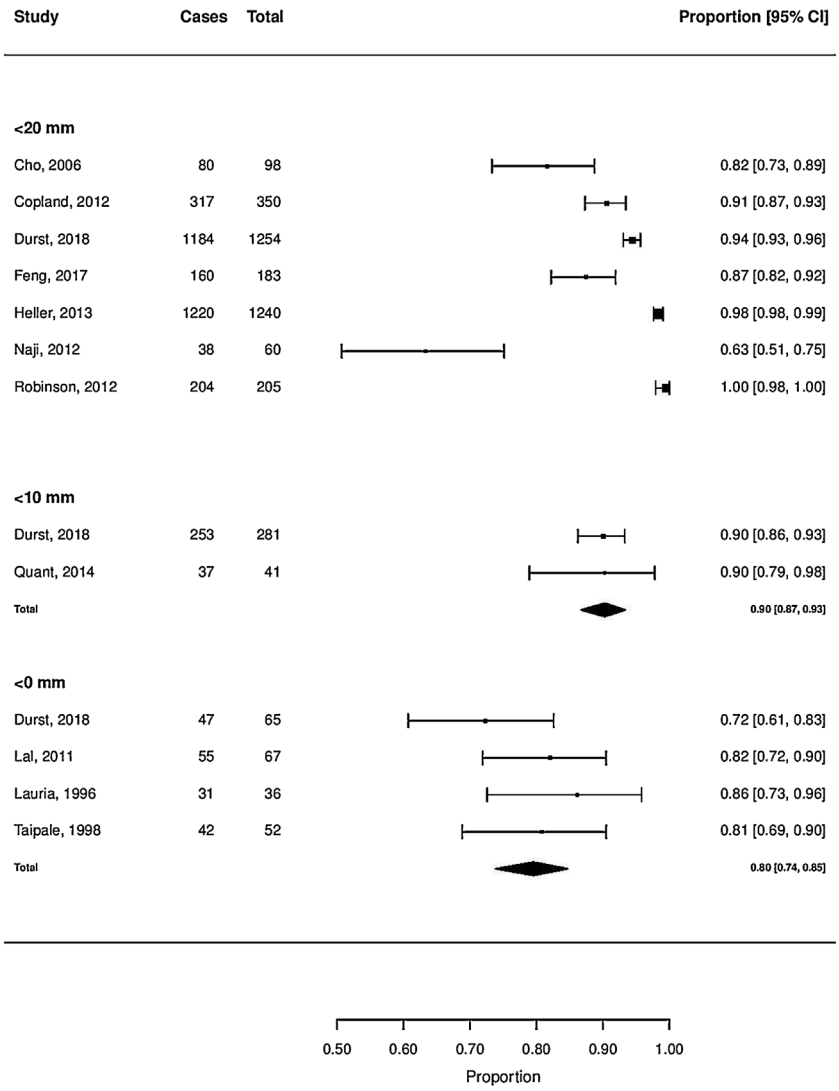

Fig. 2. Meta-analysis of the proportion of placentas with a position towards the fundus in the third trimester for the subgroups of 20 mm, 10 mm and 0 mm distance between the placenta and the internal os of the cervix.

Previous cesarean section

Four articles reported on the influence of a previous cesarean section on the placenta position in the third trimester. [50,52,56,57] For a cut-off value of < 20 mm in the second trimester, no significant difference was reported between women with and without a previous cesarean delivery (23/29 (0.79) versus 137/154 (0.89), p=0.1557] ; 13/21 (0.62) versus 25/39, (0.64) p=0.8752] and 174/188 (0.93) versus 1010/1066 (0.95), p=0.2356]). For a cut-off value of < 0 mm in the second trimester, the difference was significant between women with and without a previous cesarean section, favoring women without a previous cesarean section (11/18 (0.61) versus 44/49 (0.90), p<0.05[50]).

Discussion

Main findings

This systematic review shows that the majority (63–100%) of the second trimester low-positioned placentas, will have a higher position in the third trimester, i.e. away from the internal os of the cervix and more towards the fundus. The available evidence can only be reported as this wide range but did not allow us to pool results of all included studies or subgroups, therefore could not determine a cut-off value for the distance between the placenta and the internal os of the cervix in the second trimester that identifies all anteriorly and posteriorly located low-lying placentas in the third trimester. Anterior placentas seem to have a location towards the fundus more often and a prior cesarean section has no influence except for women with a placenta overlapping the internal os of the cervix. However, data on both matters is still limited and only described in a few studies.

Strengths and limitations

'Placental migration' is a well-known phenomenon and a subject that is discussed in numerous articles. This is the first review however, that collects all information concerning the final position of the placenta in the third trimester and the influence of the placental side and prior cesarean delivery. Since placenta previa and low-lying placentas have a relatively low incidence, articles concerning the migration thus far mainly described small cohorts, which motivated us to perform a formal systematic review with a broad search to combine all available literature. Since we used a broad search strategy with checking of cross-references and did not apply language restrictions, it is unlikely that we missed any important literature on this topic. We assessed study quality according to the recommended criteria and found that all studies, prospective and retrospective, were of good quality. Also, the majority of our included studies (80%) was prospective.

We aimed to identify the IOD cut-off value with a sensitivity of 100%, i.e. one that identifies all placentas with a low position in the third trimester, with the least amount of unnecessary follow-up ultrasounds. Here we encountered several limitations: first, there was substantial heterogeneity among the included articles despite our explicit inclusion and exclusion criteria. Various articles used different IOD cut-off values for which follow-up ultrasound was indicated and different classifications for describing the position of the placenta in the third trimester. Not all studies classified the placental position in the third trimester as normal (IOD > 20 mm), so their results showed indication of any placental migration between trimesters but not if a normal position of the placenta was eventually found. Because of this heterogeneity, we could only combine groups of studies that used similar definitions but not the results of all studies. In addition, within these groups there often was too much heterogeneity in the study results (migration rate) so that pooling of the results was not appropriate. Second, most studies did follow-up on all women with an IOD below a specific cut-off value (for example all women with IOD < 20 mm) without presenting the result for different 'test' groups (for example, <10 mm and >10 mm). Therefore, we did not have any information about false-negatives and sensitivity could not be extracted or calculated.

In our review, we aimed to distinguish between anteriorly and posteriorly located placentas and women with and without prior cesarean section. However, not all articles reported the placental location to be anterior or posterior and again different values were used as cut-off value for follow-up. Also, only few articles mentioned a prior cesarean section limiting our conclusions concerning this issue.

Moreover, we included studies which used either transabdominal and/or transvaginal ultrasound in the second trimester. Although recent research has shown that for patients with a high suspicion of placenta previa a transabdominal ultrasonography has a sensitivity and specificity comparable with transvaginal sonography. However, using transabdominal ultrasonography alone may result in high false-negative results, therefore the studies in our review using transabdominal ultrasound may be less representative. [58]

In line with the vast heterogeneity in the included studies that hampered outcome analyses, we could not assess publication bias. In the traditional funnel plot, the treatment or exposure effect estimated from individual studies is plotted against a measure of weight such as study size or precision. However, the outcome measure in our study is a proportion rather than a treatment or exposure effect and creating a funnel plot for the assessment of publication bias is not possible. In addition, there was too much heterogeneity among the included studies to establish the true underlying value. But even if this would have been possible, experts have found that visually interpreted or statistically tested asymmetry of a funnel plot does not accurately point to publication bias. [59,60]

We aimed to find answers to a relevant clinical question. The findings of our review indicate the present state of available evidence. It is important to note that based on these studies we are not able to provide these answers. This emphasizes the necessity for high-quality, prospective studies in which all women with IOD < 20 mm are followed until delivery and results of final placental position, or even delivery outcomes, are reported according to second trimester IOD.

Comparison with existing literature

In this review, most second trimester low-positioned placentas did no longer meet up to that definition in the third trimester, due to so called 'migration'. Various hypotheses considering the etiology of migration are known. One of these is trophotropism, the process of atrophy of thin placental margins due to a poor vascular supply in the lower uterine segment. In contrast to the lower uterine segment with poor vascular supply causing atrophy, the blood supply to the cervix is improved during pregnancy, which makes atrophy, and thus migration, less likely to occur in placenta previa, which is covering the internal os of the cervix. [48]

Another possible explanation is called dynamic placentation, in which it is hypothesized that the anterior uterine wall expands more than the posterior wall. This can relate to a possible higher migration rate of anterior placentas since the lower uterine segment will lengthen due to elongation and hypertrophy during pregnancy, causing enlargement of the uterus on the anterior side. [61]

No strict conclusions could be drawn on the influence of the placental side when considering placental migration. One study did not show any significant difference between anterior and posterior placentas and three studies did show a difference between anteriorly and posteriorly located placentas but two were

favoring anterior placentas and one favored posterior placentas. One of the included articles suggested that anteriorly located placentas had a better prognosis, since the incidences of a cesarean section, a premature delivery and vaginal spotting during pregnancy were significantly higher in the posterior group in their cohort of 98 cases. [48] Another cohort which was not eligible for our review, suggested rescanning of an early low-lying placenta needs to be restricted to the posterior group, since the posteriorly located placentas included in their cohort needed a cesarean delivery [37]. In the one study which favored posteriorly located placenta previa, the placenta location did not show any difference in pregnancy outcome [57].

The migration of a second trimester low-positioned placenta is multifactorial. A marginal sinus, the migration rate in mm per week and a previous cesarean delivery seem to be of influence. It has been suggested that a low-lying placenta accompanied by a marginal sinus, defined as a hypo echogenic area with slow blood flow on ultrasound, hardly moves upwards at the end of the third trimester comparing to placentas without a marginal sinus. This can lead to a higher risk of antepartum bleeding and the need for an emergency caesarean section. [62] It has also been suggested that placental migration in mm per week can differ between women and that women with lower mean rates for placenta migration in mm per week are more often in need of a cesarean delivery because of a low-positioned placenta in the third trimester of pregnancy [17,63].

We found that with a cut-off value of < 20 mm a previous cesarean delivery did not influence the IOD of the placenta in the third trimester. However, with a cut-off value of < 0 mm in the second trimester a difference was observed between women with and without a previous cesarean delivery. Placentas of women with a previous cesarean delivery more often remained located at a distance of < 0 mm in the third trimester than placentas of women without a precious cesarean delivery. Thus, it could be hypothesized that scarred endometrium influences the chance of a position towards the fundus of an anteriorly located placenta in the third trimester. [52] This hypothesis has been confirmed by other studies that showed that women with a prior cesarean delivery and a scarred lower uterine segment as a result had a lower likelihood of a position towards the fundus in the third trimester. One of the studies did distinguish in placental side and only the anterior placentas appeared to have a lower likelihood of migration [50,64]. Future studies on placental migration should report a previous cesarean delivery as well as anterior or posterior placental location.

Conclusions and implications

In conclusion, the majority (63–100%) of the second trimester low-positioned placentas will have a position more towards the fundus in the third trimester. However, a cut-off value that includes all women with a persisting low-positioned placenta could not be defined. Also, the influence of the placental side on placental migration is not clear. Large prospective studies are needed to determine this cut-off value that allows for identification in the second trimester of all women at increased risk during pregnancy and delivery and to safely reduce the number of follow-up ultrasounds Future studies should report sensitivities and false-positive rates according to IOD and present separate results for anteriorly and posteriorly located placentas and women with or without a previous cesarean delivery.

Condensation

Second trimester low-positioned placentas mostly have a higher position in the third trimester. Posterior placentas seem persist more often that anterior placentas.

Contribution to authorship

All authors contributed significantly to this work by either participating in the search, supporting in analyses and writing or revising this manuscript.

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Declaration of Competing Interest

B.W. Mol is supported by a NHMRC Practitioner Fellowship (GNT1082548); B.W. Mol reports consultancy for ObsEva, Merck Merck KGaA and Guerbet; The remaining authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.ejogrb.2019.06.020.

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