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Differences in cervical length during the second trimester among normal weight, overweight and obese women: A systematic review and meta-analysis☆

Michail Panagiotopoulos *, Vasilios Pergialiotis, Konstantina Trimmi, Antonia Varthaliti, Antonios Koutras, Panagiotis Antsaklis, Georgios Daskalakis

1st Department of Obstetrics and Gynecology, Alexandra Hospital, National and Kapodistrian University of Athens, Greece

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ABSTRACT

Objective: Maternal obesity has been previously linked to increased risk of preterm birth; however, the actual pathophysiology behind this observation remains unknown. Cervical length seems to differentiate among overweight, obese and extremely obese patients, compared to normal weight women. However, to date the actual association between body mass index and cervical length remains unknown. In this systematic review, accumulated evidence is presented to help establish clinical implementations and research perspectives.
Methods: We searched Medline, Scopus, the Cochrane Central Register of Controlled Trials CENTRAL, Google Scholar, and Clinicaltrials.gov databases from inception till February 2023. Observational studies that reported on women undergone ultrasound assessment of their cervical length during pregnancy were included, when there was data regarding their body mass index. Statistical meta-analysis was performed with RStudio. The quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS).
Results: Overall, 20 studies were included in this systematic review and 12 in the meta-analysis. Compared to women with normal weight, underweight women were not associated with increased risk of CL $<$ 15 mm or $<$ 30 mm and their mean CL was comparable (MD −1.51; 95% CI −3.07, 0.05). Overweight women were found to have greater cervical length compared to women with normal weight (MD 1.87; 95% CI 0.52, 3.23) and had a lower risk of CL $<$ 30 mm (OR 0.65; 95% CI 0.47, 0.90).
Conclusion: Further research into whether BMI is associated with cervical length in pregnant women is deemed necessary, with large, well-designed, prospective cohort studies with matched control group.

Introduction

Two main causes of pregnant morbidity are obesity and cervical insufficiency [1]. The prevalence of obesity is increasing, with more than one in five women of reproductive age being classified as obese (body mass index, BMI $>$ 30 kg/m^2) [2]. Compared to normal weight women, obese women seem to undergo a decreased rate of spontaneous premature birth [3]. Prior research indicates that maternal obesity during pregnancy is linked to a higher need for labor induction, prolonged labor times, greater oxytocin and misoprostol dosages, and crucially, more cesarean sections [4,5]. In a nationwide cohort study that evaluated pregnancy outcomes from 1.5 million deliveries, researchers observed that women with grade 2 and 3 obesity (BMI >35) had substantially larger risk of spontaneous preterm delivery, including extremely preterm and very preterm delivery [6]. It is still unclear how exactly obesity may affect labor duration, incidence of preterm birth, and gestational age at birth [7]. However, there are few contemporary studies that report a higher incidence of PPROM, chorioamnionitis and early delivery following PPROM among obese patients [8–10] indicating that obesity should be regarded a significant factor that directly affects the pregnancy course. Considering the mechanical effect of the increased intraabdominal pressure that is exerted by obesity researchers have examined the impact of maternal BMI during the first trimester of pregnancy and observed that it affects second-trimester cervical length after accounting for numerous confounding factors [11]. To date, however, consensus in this field is still missing.

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* Correspondence to: Lourou 2-4, 11528 Athens, Greece.
E-mail address: mipanag@otenet.gr (M. Panagiotopoulos).

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The purpose of the present systematic review is to evaluate if body mass index affects cervical length (CL). The assessment will be evaluated from studies that measure cervical length during second trimester screening.

Material and methods

Protocol and registration

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The study was based in aggregated data that have been already published in the international literature. Patient consent and institutional review board approval were not retrieved as they are not required in this type of studies. The protocol of the study was prospectively registered with the PROSPERO database of systematic reviews (ID CRD42021293835).

Eligibility criteria

Eligibility criteria for the inclusion of studies were predetermined. Observational studies (case control, cohort studies, prospective or retrospective) that reported on women undergone ultrasound assessment of their cervical length during pregnancy (second trimester screening preferred) were included, when there was data regarding their body mass index. Exclusion criteria include assessment of cervical length in non-pregnant women, women with an a-priori indication for cesarean delivery and women with multiple gestation.

Information sources and search strategy

Two authors (V.P and M.P.) searched Medline (1966–2023), Scopus (2004–2023), Clinicaltrials.gov (2008–2023), Cochrane Central Register of Controlled Trials CENTRAL (1999–2023) and Google Scholar (2004–2023) along with the reference lists of electronically retrieved full-text papers. The date of the last search was set at February 1, 2023. No date restrictions were applied. Articles were limited to English language. The search strategy included the text words “Body Weight; Obesity; Overweight; Body Mass Index; bmi; Cervical Length Measurement; Cervix Uteri; Uterine Cervical Incompetence”.

Studies were selected in three consecutive stages. Following deduplication, the titles and abstracts of all electronic articles were independently screened by two authors (V.P. and M.P) to assess their eligibility. The decision for inclusion of studies in the present meta-analysis was taken after retrieving and reviewing the full version of articles that were considered potentially eligible. Discrepancies that arose in this latter stage were resolved by consensus from all authors.

Study selection and data extraction

Outcome measures were predefined during the design of the present systematic review. Data extraction was performed using a modified data form that was based in Cochrane`s data collection form for intervention reviews for RCTs and non-RCTs.

The outcomes of our study were mean cervical length during the second trimester and the incidence of short cervical length (both $<$ 25 mm and $<$ 15 mm).

Assessment of risk of bias and quality of evidence

The quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) by two reviewers (M.P. & A.K.) [13]. Items assessed are included in three parts: selection (four items), comparability (two items) and outcomes (three items). A maximum of nine stars can be allocated to each study. The quality of each study was described as high (score 7–9), moderate (4−6) or poor (0−3).

Synthesis of results

Statistical meta-analysis was performed with RStudio using the meta and metafor functions (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/). Statistical heterogeneity was not considered during the evaluation of the appropriate model of statistical analysis as the anticipated methodological heterogeneity of included studies did not leave space for assumption of comparable effect sizes among studies included in the meta-analysis [14]. Confidence intervals were set at 95%. We calculated pooled mean differences (MD) and 95% confidence intervals (CI) with the Hartung-Knapp-Sidik-Jonkman instead of the traditional Dersimonian-Laird random effects model analysis (REM). The decision to proceed with this type of analysis was taken after taking into consideration recent reports that support its superiority compared to the Dersimonian-Laird model when comparing studies of varying sample sizes and between-study heterogeneity [15]. When variables were expressed as median (range), median (interquartile range) or interquartile range and sample size transformation were performed to acquire the mean and standard deviation to include the studies in the meta-analysis [16].

Prediction intervals

Prediction intervals (PI) were also calculated, using the metafunction in RStudio, to evaluate the estimated effect that is expected to be seen by future studies in the field. The estimation of prediction intervals takes into account the inter-study variation of the results and express the existing heterogeneity at the same scale as the examined outcome.

Subgroup analysis

Subgroup analysis was designed following the retrieval of studies as several articles evaluated differences among various groups of maternal obesity. Therefore, we performed subgroup analysis according to four groups: underweight women (BMI < 18.5 kg/m^2), women with normal weight (BMI 18.5 - 24.9 kg/m^2), overweight women (BMI 25 - 29.9 kg/m^2) and obese women (BMI > 30 kg/m^2).

Results

Selection, characteristics and risk of bias of studies

A total of 20 studies were identified for inclusion in the review. The search of Medline, Scopus and ClinicalTrials.gov databases provided a total of 1260 results. After adjusting for duplicates 1161 citations remained. Of these, 1135 studies were discarded because after reviewing the titles and abstracts, these papers clearly did not meet the criteria. One additional study was discarded because full text was not available. The full text of the remaining 25 studies was examined in more detail, after which 5 studies did not meet the inclusion criteria. (Fig. 1).

Therefore, 20 studies were included in this systematic review and 12 in the meta-analysis [3,17–27]. The characteristics of included studies are summarized in Table 1. The included studies were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) and found to be of moderate to high quality. (Table 1).

Synthesis of results

Underweight (BMI $<$ 18.5)

The mean difference of CL between underweight and normal weight women was not statistically significant (MD −1.51; 95% CI −3.07, 0.05) (Fig. 2). Compared to women with normal weight, underweight women were not associated with increased risk of CL $<$ 15 mm (Fig. 3) or CL $<$ 30 mm (Fig. 4).

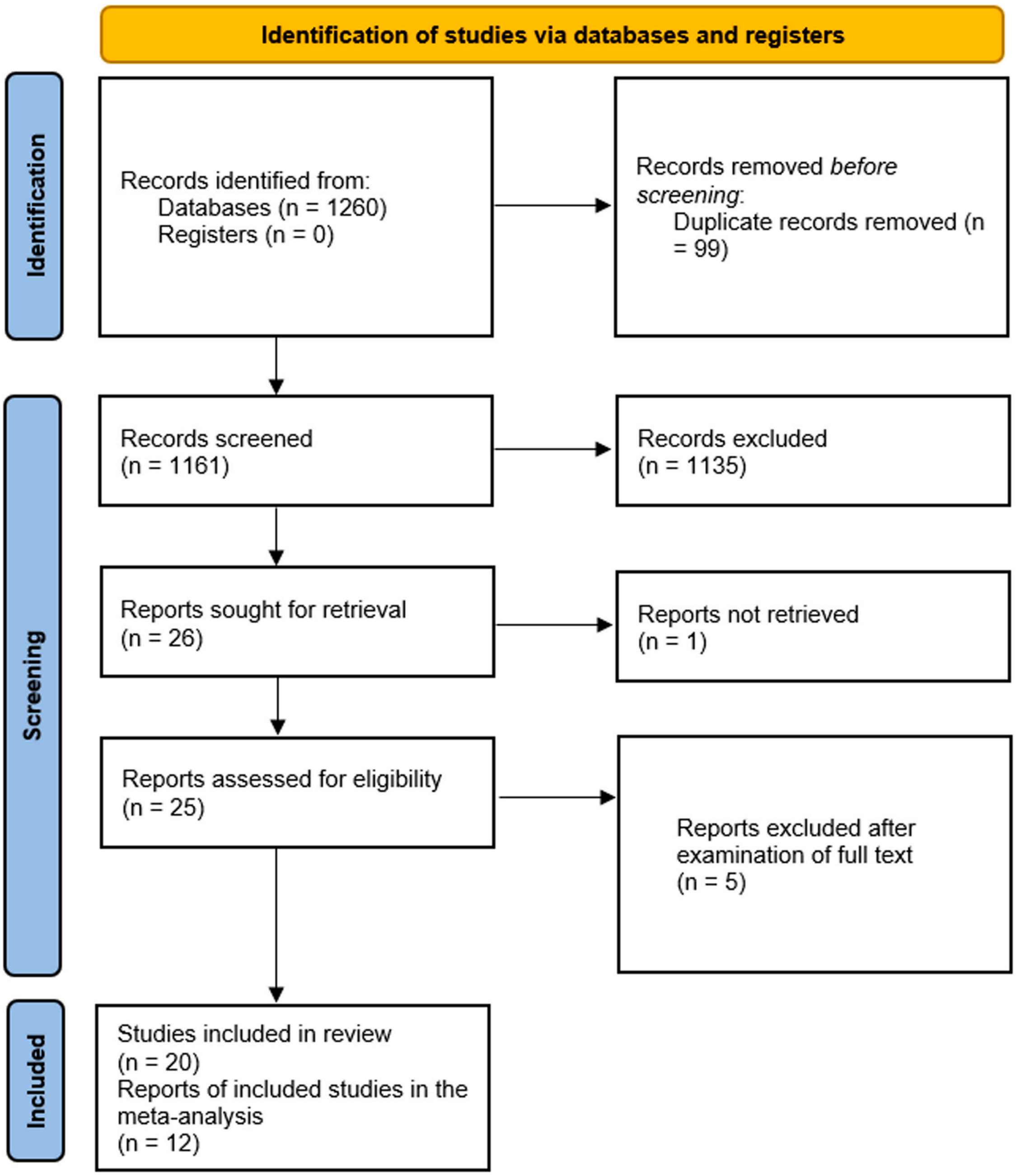

Fig. 1. Flow chart.

Overweight (BMI > 25)

Women with BMI > 25 kg/m^2 were found to have greater cervical length compared to women with normal weight (MD 1.87; 95% CI 0.52, 3.23) (Fig. 5), which remained after removing from the analysis two studies that included women with history of prior SPTB (MD 2.08; 95% CI 0.57, 3.59). Subgroup analysis according to BMI group is presented in Fig. 5.

Regarding the incidence of CL < 30 mm, overweight women had a statistically significant lower risk compared to women with normal weight (OR 0.65; 95% CI 0.47, 0.90) (Fig. 6). However, after removal of two studies that included women with history of prior SPTB, there was no statistically significant difference (OR 0.63; 95% CI 0.35, 1.11).

Sensitivity analysis

One study was evaluated as a potential outlier in the analysis of mean differences among obese and normal weight women (Kandil et al.). After omitting it the overall mean difference among overweight/obese women and normal weight women was non-significant (MD 1.50, 95% CI 0.65, 2.35). The investigation for potential p-hacking revealed and evidential value of mean differences among these groups, whereas data were not sufficient to allow definitive results for women with a CL< 30 and < 15 mm.

Discussion

Principal findings and comparison with existing literature

Our main hypothesis on this study was that cervical length during pregnancy was related with BMI and in extension, with the implications CL has during the course of pregnancy. As far as our analysis goes, the effect BMI had on cervix length in the underweight and normal weight

Table 1
Characteristics of included studies. (NOS: Newcastle-Ottawa Scale).

Study	Study type	Country	n	CL assessment	Inclusion criteria	Exclusion criteria	NOS score
Marquart 2022	Cross-sectional	Brazil	7844	Transvaginal ultrasound	Singleton pregnancy, 18-22 + 6 weeks of gestation	Women with painful contractions, vaginal bleeding,cerclage during current pregnancy before the screening, ruptured membranes diagnosed before screening, severe liver disease, cholestasis during this pregnancy, previous or current thromboembolism, placenta previa, cervical dilation greater than 1 cm, twin gestations, and major fetal malformation or at least one fetus and stillbirth	7
An 2021	Prospective cohort	China	4843	Perineal ultrasonography	Age > 18 years, 22–24 gestational weeks, planned to deliver at the hospital		8
Salem 2021	Prospective cohort	Egypt	188	Transvaginal ultrasound	Age 20-35 years, BMI (20-32 kg/m2), gestational age (20-24) weeks, primigravida, and singleton pregnancy.	Smokers, congenital anomalies of uterus and cervix (assessed by ultrasonography), multiple pregnancies, placental abnormalities, past history of cervical operations, and the presence of cervical abnormalities.	6
Venkatesh 2020	Retrospective	USA	356	Transvaginal ultrasound	≥ 1 prior SPTB < 37 weeks of gestation, a singleton pregnancy, and initiated 17-OHPC at 16-20 weeks of gestation and had a transvaginal CL assessment 14-< 23 weeks of gestation		8
Kandil 2017	Prospective cohort	Egypt	100	Transvaginal ultrasound	Low risk primigravid women, age 25–35 year-old, singleton pregnancies, 20–22 weeks of gestation.	(1) first trimester bleeding, low lying placenta or evidence of utero-placental insufficiency; (2) disparity in gestational age of more than 1 week as calculated by the first trimester scan and menstrual gestational age; (3) myomatous or malformed uterus; (4) multiple pregnancy and hydramnios; (5) premature rupture of membranes; (6) cervical incompetence; (7) medical disorders that may affect negatively the duration of gestation, such as diabetes mellitus and pregnancy-induced hypertension and recurrent urinary tract infections.	8
Palatnik 2017	Retrospective cohort	USA	18100	Transvaginal ultrasound	Age > 18 years, singleton gestation, mid-trimester ultrasound for CL measurement, and delivered at the study institution	prior SPTB or stillbirth	6
Han 2011	Retrospective	South Korea	608	3D ultrasonography	Pregnant women in their second and third trimesters (19–39 weeks)		6
Ehrenberg 2009	Retrospective	USA	253	Transvaginal ultrasound	Women with singleton pregnancies at increased risk for preterm birth (history of one or more spontaneous preterm deliveries between 20 and 36 weeks of gestation, or second-trimester vaginal bleeding in the current pregnancy)	Women receiving or planning to use home uterine activity monitoring, prophylactic tocolytic therapy, or with a cervical cerclage in place, those with placenta previa or major fetal anomaly.	6
Hendler 2005	Retrospective	USA	2910	Unspecified	23-24 weeks of gestation	Multifetal gestation, major fetal anomalies, history of cervical cerclage in the current pregnancy and placenta previa.	5
Erasmus 2005	Retrospective	South Africa	1920	Transvaginal ultrasound	Women attending routine antenatal clinics		7
Palma-Dias 2004	Cross-sectional	Brazil	1131	Transvaginal ultrasound	Women attending routine prenatal care service	Women with in situ cervical cerclage, severe fetal malformations or polyhydramnios	7
Liabsuetrakul 2002	Prospective cohort	Thailand.	144	Perineal ultrasonography	Singleton pregnant women who had an accurate gestational age determined from the last menstrual period (LMP) and confirmed by sonography before the second trimester	Women who had medical diseases or previous cervical operations	7

group was inconsequential. However, when the BMI increased over 25, there appears to be an elongation of the cervix. The statistical importance of this result appears to be significant and as mentioned later there is an increasing number of studies in the bibliography that tend to the same conclusion.

Obesity is by many considered the deadly disease of our century with many genetic, physical, psychological and even socioeconomical aspects and has been well linked to cardiovascular disease, diabetes, hypertension, and many other comorbidities [28,29]. A well accepted classification of obesity is done with extensive use of Body mass index (BMI) that categorizes adults as underweight, normal weight or overweight (or obese) based on height and tissue mass. With the rates of obesity consistently rising -even more so after the Covid- 19 pandemic-, an expanding field of research is lying ahead [30]. Obese pregnant women

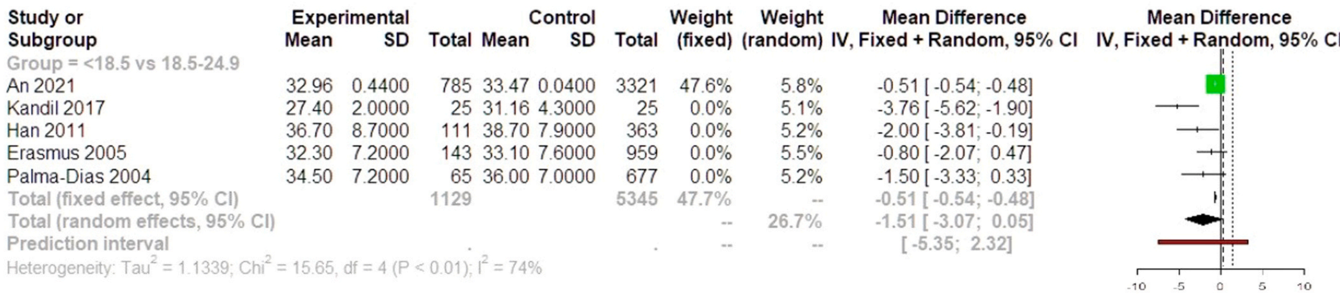

Fig. 2. Forest plot of mean differences of CL between underweight and normal weight women (Vertical line = "no difference" point between the two groups; Diamonds = pooled mean difference and 95% CI for all studies; Horizontal black lines = 95% CI; Horizontal red line = pooled 95% prediction intervals).

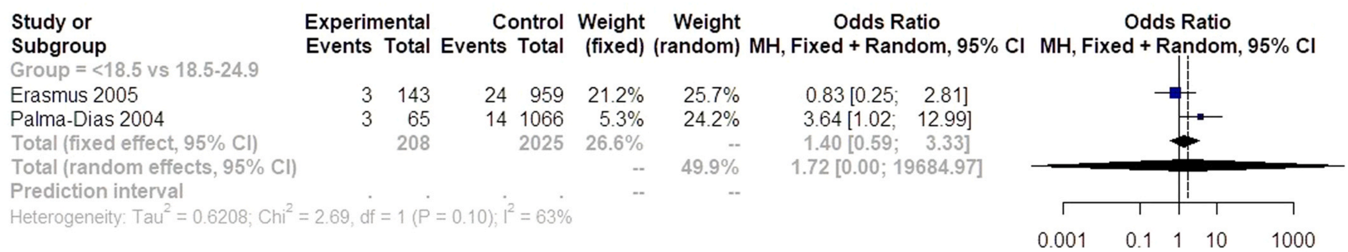

Fig. 3. Forest plot of odds ratios of having CL < 15 mm between underweight and normal weight women. (Vertical line = "no difference" point between the two groups; Diamonds = pooled mean difference and 95% CI for all studies; Horizontal black lines = 95% CI; Horizontal red line = pooled 95% prediction intervals).

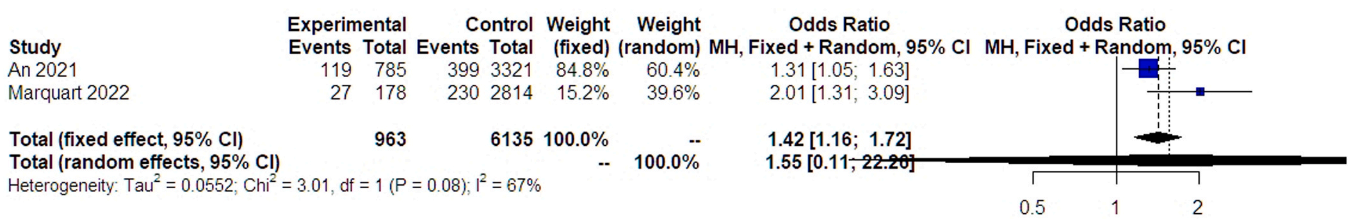

Fig. 4. Forest plot of odds ratios of having CL < 30 mm between underweight and normal weight women. (Vertical line = "no difference" point between the two groups; Diamonds = pooled mean difference and 95% CI for all studies; Horizontal black lines = 95% CI; Horizontal red line = pooled 95% prediction intervals).

are also considered a higher-risk population, since they tend to have increased rates of miscarriage, diabetes, preeclampsia/eclampsia, intraamniotic infection, induced labour and caesarean section deliveries [31].

The cervix's role in pregnancy and in successfully completing labor is paramount. There are studies that draw a well-defined connection between a short CL length during the second trimester scan and a higher risk of preterm birth [32,33]. Consequently, any aspect that can affect CL deserves to be further investigated.

The results of our study indicate that a higher BMI is associated with larger cervical length is backed up by several other studies. To be more precise, in 1998, Heath et al. described in their study of 2702 women that cervical length was shorter in women with a low ponderal index (ponderal index is an alternative of the BMI index, calculating the relation between mass and height) [34]. In a large, nationwide, prospective study of more than 5000 women in Netherlands the researchers analyzed possible association between cervical length and a variety of maternal features. They discovered that CL increases with BMI, both in the univariate and the multivariate analysis [35]. Charlotte et al., performed a retrospective descriptive study in 209 women, showing that lower BMI was associated with a shorter cervix, while maternal obesity favored a longer cervix length [36]. Concurrent with that was also a secondary analysis of a case-control study of 391 pregnant women, where it was found that for each 1.0 kg/m2 added to the BMI, the length of the cervix increased by 0.25 mm (95% CI: 0.14–0.36) [37]. Some pregnancy related risks, such as cervical incompetence [OR 0.55 (0.48; 0.63); $p < 0.001$] and preterm labour [OR 0.47 (0.43; 0.51); $p < 0.001$], were found to be less common in obese pregnant women [38], while in another study a BMI < 30 seems to elevate the risk of SPB (4,9%), compared to a BMI > 30 [39]. In agreement, Miller et al. in a retrospective cohort study found that the likelihood of a longer CL increased if the women had a larger BMI. [40].

Currently, it is well established that obese patients have increased intra-abdominal pressure which is within the range of normal limits (does not fall in the range of intra-abdominal hypertension) [41,42] and that transient increases in intraabdominal pressure predisposes to significant reduction in cervical length measurement [43]. Considering this, it would be easy to assume that overweight and obese women would rather have smaller cervices, which directly opposes the current research. In view of these assumptions, it must be stated that the actual pathophysiology behind this evidence remains unknown, as it is difficult to assume that a high pre-pregnancy intraabdominal pressure results in elongated cervical length, which could potentially protect against preterm birth. Perhaps a fusion of physiological and endocrinological reasons create a different environment in comparison to normal weight counterparts [44].

On a different note, it should be highlighted that a large single-center retrospective cohort study that involved 3296 women indicated the absence of an association between maternal BMI and cervical length measured between 20 and 24 weeks of gestation [45].

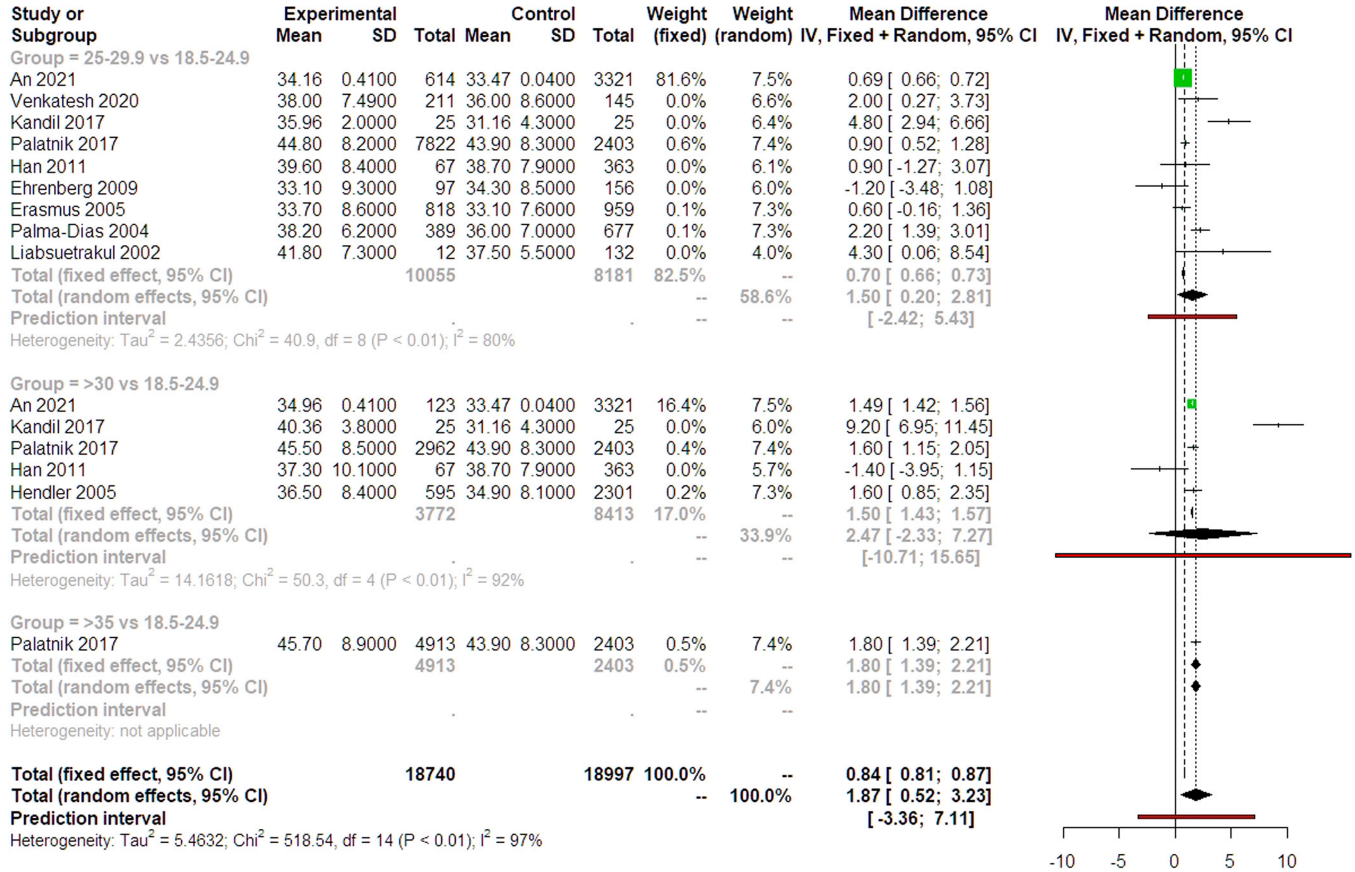

Fig. 5. Forest plot of mean differences of CL between women with BMI > 25 kg/m^2 (subgrouped according to BMI) and normal weight women. (Vertical line = "no difference" point between the two groups; Diamonds = pooled mean difference and 95% CI for all studies; Horizontal black lines = 95% CI; Horizontal red line = pooled 95% prediction intervals).

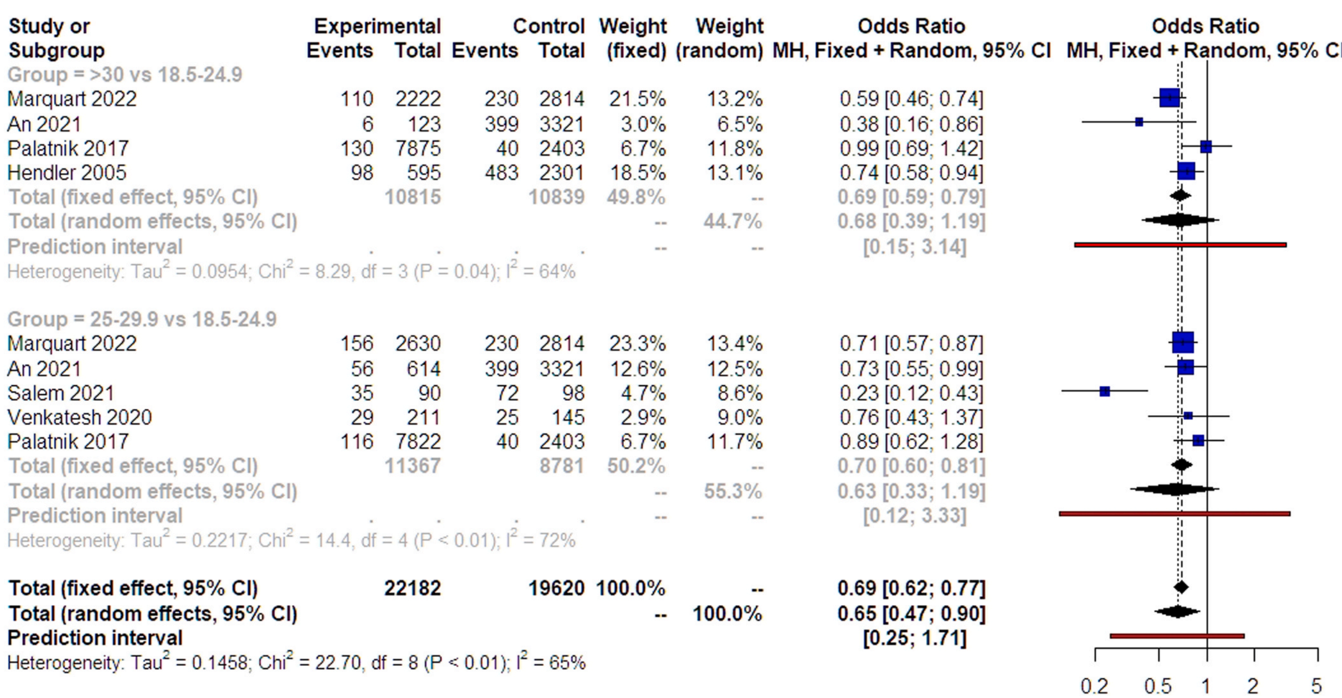

Fig. 6. Forest plot of odds ratios of having CL < 30 mm between women with BMI > 25 kg/m^2 (subgrouped according to BMI) and normal weight women. (Vertical line = "no difference" point between the two groups; Diamonds = pooled mean difference and 95% CI for all studies; Horizontal black lines = 95% CI; Horizontal red line = pooled 95% prediction intervals).

Strengths and limitations

One of the main strengths of the current study is the fact that it summarizes all the available knowledge regarding the association between BMI and cervical length, while at the same time identifying any potential openings and chances for future investigation and research. On top of that, the extensive electronic search performed, and care taken in data extraction and analysis can only be added to the strong points of this study.

On the other hand, caution must be taken when analyzing meta-analyses, since errors may be performed during the analysis and the heterogeneity of studies may lead to unfavorable outcomes and results. This heterogeneity is one main limitation, as the timing of BMI calculation, the mode of CL assessment and the personnel performing it were not clearly specified in many of the studies. Furthermore, extrapolating data to populations not included in the studies is also a point to be taken into account, as the analysis of other geographic or ethnic factors may be considered as confounding. Finally, statistically important differences between the subgroups may not be deemed as significant as well as the scarcity of studies on this topic can also affect the results. Accordingly, the risk of bias affecting the data should be held in mind.

Implications for future work

The need for future research on this subject is clear. Large, well-designed, prospective cohort studies with matched control groups are required. Study population should be stratified according to BMI and be observed over the whole duration of pregnancy in order to assess cervical length, as well as other peripartum outcomes. Cervical length should be assessed using transvaginal ultrasound between 16 and 24 weeks of gestation according to the recommendations of Society for Maternal-Fetal Medicine (SMFM) [46].

Conclusions

Although the available published data seems to be non-conclusive, it should be noted that physicians and health care providers should not rest on factors such as BMI or race to adequately screen patients for short cervical length. Transvaginal ultrasound remains the gold standard and should be offered to all pregnant women during second-trimester evaluation. Further research into whether maternal characteristics are associated with cervical length in pregnant women and all the implications this entails is deemed necessary.

Disclosure

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CRediT authorship contribution statement

Panagiotopoulos Michail: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Pergialiotis Vasilios:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Trimmi Konstantina:** Writing – original draft, Investigation. **Daskalakis George:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Koutras Antonios:** Writing – original draft. **Antsaklis Panagiotis:** Writing – review & editing, Supervision, Investigation. **Varthaliti Antonia:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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