

**Review Article** 

# Review of Biomechanical Deviations among Non-pregnant, Pregnant, and Postpartum Cohorts

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#### Abstract

**Objective:** This review analyzed available studies on biomechanical changes during the pre-, in-, and post-pregnancy periods.

Data sources: In the electronic databases of PubMed, Scopus, and Cochrane from inception until June 2, 2021

**Study eligibility criteria:** 1) the research object of the literature is healthy pregnant women; 2) the research direction is in the range of biomechanics, which can be related to the trunk, lumbar spine, hip joint, knee joint, ankle joint, wrist joint, foot, muscle strength, muscle endurance, joint strength, plantar pressure, and motion analysis; 3) with full text; 4) written in English or Chinese and 5) cohort studies comparing pregnant women with the same group of women in the pre-pregnancy period or with non-pregnant women.

Study appraisal and synthesis methods: Using National Institutes of Health quality assessment tool for observational cohort and cross-sectional studies to assessment the quality of the reviewed articles. Synthesized the general information (authors, publication years, country where the studies were conducted etc.), age of the studied subjects, investigated periods, sample size, objectives, study ammetersers, measurement tools, and outcomes of reviewed studies.

**Results:** Duplicate results were removed, the search returned 2918 reports. Fourteen studies met the selection criteria, and were included in this analysis.

**Conclusion:** These studies revealed biomechanical deviations in body stability, motion patterns, and gait modes during these three periods. Regarding research content, there are insufficient studies on certain critical biomechanical aspects, such as the kinetic parameters of the inner body, which are the most direct factors related to musculoskeletal problems. According to the National Institutes of Health quality assessment tool for observational cohort and cross-sectional studies, a more comprehensive and explicit understanding of pregnancy biomechanics can be expected.

**Keywords:** Pregnancy; Center of Pressure (COP); Kinematic; Kinetic; Balance; Stability; Motion Patterns; Gait Modes

# Introduction

Pregnancy is one of the most common and critical events in the life of women. The entire pregnancy period can categorized into three trimesters (1-12 weeks, 13-26 weeks, and 27 to the end) [1]. During pregnancy, women experience substantial changes in their bodies, such as physiology, morphology, and hormonal systems. Body laxity increases because of the relaxin hormone and reaches its maximum level in the second trimester [2]. The physiological structure of the chest as well as trunk geometry and muscle function change during pregnancy to adapt to fetal growth. These changes affect the range of motion of various body segments and sports performance [3], possibly resulting in extended discomfort and pain. Studies have shown that 90% of pregnant women suffer from back pain, 50% complain of waist pain, 20% complain of pelvic and genital pain, and 20% complain of lumbar radiculopathy [4]. The rectus abdominis muscle plays an essential role in trunk movement, pelvic stability, and restraint of the contents of the abdominal cavity. The separation of the rectus abdominis occurs during pregnancy and the first week after delivery. The long-term separation of the rectus abdominis adversely affects the body shape and position of the internal organs.5 Physical and physiological problems can result in emotional and sleep problems in pregnant women.

Because pregnancy is a contraindication for many treatments

and drugs, the management of these problems is still challenging, and current treatment methods are not satisfactory [4, 6-8]. Physical exercise, body orthoses, and medicine are commonly recommended for the prevention and treatment of pregnancy problems and body function recovery during the postpartum period. However, debates exist among studies on the effectiveness and safety of these treatments. In a review study, interventions to prevent and treat pelvic and back pain, such as increasing the amount of exercise and using specially designed pillows, were found to significantly reduce waist pain [4]. However, some studies found that the outcomes of these treatments were unsatisfactory [9]. The postpartum rehabilitation protocols have not been fully explored. Evaluation of the effects of interventions is critical for determining a

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fitness protocol. Biomechanical research on pregnancies have been conducted through various approaches. However, there are few studies that provide comprehensive knowledge, cutting-edge developments, and research and practical gaps in this area. Therefore, this study aims to comprehensively review biomechanical studies on non-pregnancy, pregnancy, and postpartum periods, preparing for future research on the pregnant cohort.

## Method

#### **Data Sources and Searches**

Articles were searched in the electronic databases of PubMed, Scopus, and Cochrane from inception until June 2, 2021. Pregnant/ pregnancy and biomechanics were used as searching keywords, and we obtained 117 literature from Pubmed, 2891 from Scopus, and 11 from Cochrane. Duplicate results were removed, and 2918 studies were finally collected.

#### Selection Criteria for the Analysis

The included pieces of literature were required to meet the following criteria: 1) the research object of the literature is healthy pregnant women; 2) the research direction is in the range of biomechanics, which can be related to the trunk, lumbar spine, hip joint, knee joint, ankle joint, wrist joint, foot, muscle strength, muscle endurance, joint strength, plantar pressure, and motion analysis; 3) with full text; and 4) written in English or Chinese. Two authors independently performed the selection using predetermined criteria, and a third and fourth researchers resolved disagreements through discussion or arbitration until consensus was reached.

By browsing article titles and abstracts, 821 works of literature with full text were selected for further confirmation. After reading the full text, 100 studies were confirmed. Figure 1 shows the selection procedure. The classifications of the selected 100 studies are listed in Table 1. In these studies, the postpartum cohort was used as the control group. Considering that the body anatomy and functions might not have completely recovered to the pre-pregnancy level several months after delivery, it might not be reasonable to set the postpartum period as the control group. An additional selection criterion was added for this review: 5) cohort studies comparing pregnant women with the same group of women in the pre-pregnancy period or with nonpregnant women. Fourteen articles were included in the final analysis (Table 2).

#### Results

#### **General Information Involved in Systematic Review Studies**

Table 2 shows the general information of the 14 reviewed studies, including the authors, years of publication, country where the studies were conducted, and titles and publishing journals.

The 14 articles were published between 2002 and 2019. Most of the articles were published in 2015. In 2010, two articles were written by the same author, based on one study from different perspectives. Five studies were conducted in the USA, two in Australia, two in Portugal, two in Japan, one in China, one in Poland, and one in Germany.

Pregnant and non-pregnant women were included in the cohort studies. Some studies explored different pregnant trimesters in one pregnant group, and used a group of non-pregnant women as controls. Other studies investigated the same group of subjects from the non-pregnant to the pregnancy period. Some studies included the postpartum period, whereas others did not.

# Age

The age range of the subjects (including control groups) was 1916-4010 years, as shown in Table 3. The investigated periods and target populations were also provided.

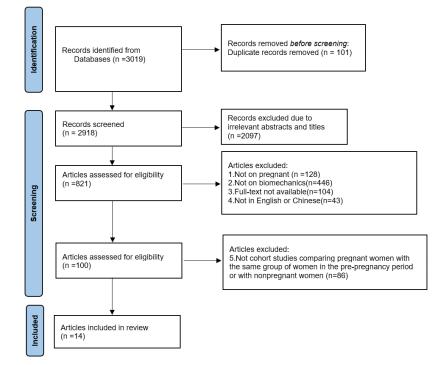


Figure 1: Flowchart of the literature search process using PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

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Table	1: The classification of selected studies.	
lable	<ol> <li>The classification of selected studies.</li> </ol>	

Book	Review papers	<b>Cross-sectional studies</b>	Randomized controlled trials	Control experiments	Cohort studies
1	8	3	2	33	52

Author	Publication years	Place	Title	Journal	Othe
Gilleard, W. Crosbie, J. Smith, R.	2002	Australia	Effect of pregnancy on trunk range of motion when sitting and standing	Acta Obstetricia et Gynecologica Scandinavica	10
Butler, E. E. Colón, I. Druzin, M. L. Rose, J.	2006	American	Postural equilibrium during pregnancy: Decreased stability with an increased reliance on visual cues	American Journal of Obstetrics and Gynecology	11
Jang, J. Hsiao, K. T. Hsiao-Wecksler, E. T.	2008	USA	Balance (perceived and actual) and preferred stance width during pregnancy	Clinical biomechanics (Bristol, Avon)	12
Mc Crory, J. L. Chambers, A. J. Daftary, A. Redfern, M. S.	2010	USA	Dynamic postural stability during advancing pregnancy	Journal of Biomechanics	13
McCrory, J. L. Chambers, A. J. Daftary, A. Redfern, M. S.	2010	USA	Dynamic postural stability in pregnant fallers and non-fallers	BJOG: An International Journal of Obstetrics and Gynaecology	14
Forczek, W. Staszkiewicz, R.	2012	Poland	Changes of kinematic gait parameters due to pregnancy	Acta Bioeng Biomech	15
Branco, M. Santos-Rocha, R. Aguiar, L. Vieira, F. Veloso, A.	Branco, M.     2013     Portugal     Kinematic analysis of gait in the second and third trimesters of pregnancy     Journal of Pregnancy       Gautar, L. Vieira, F.     Vieira, F.     Vieira     Vieira     Vieira		Journal of Pregnancy	16	
Gilleard, W. L.	2013	Australia	Trunk motion and gait characteristics of pregnant women when walking: Report of a longitudinal study with a control group	BMC Pregnancy and Childbirth	17
Betsch, M. Wehrle, R. Dor, L. Rapp, W. Jungbluth, P. Hakimi, M. Wild, M.	2015	Germany	Spinal posture and pelvic position during pregnancy: a prospective rasterstereographic pilot study	European Spine Journal	18
Zhang, Y. Lu, H. Gu, Y. Hu, N.	2015	China	Characteristics of the center of pressure progression for pregnant women during walking	International Journal of Biomedical Engineering and Technology	19
Takeda, K. Shimizu, K. Imura, M.	2015	Japan	Changes in balance strategy in the third trimester	Journal of Physical Therapy Science	20
Branco, M. Santos-Rocha, R. Aguiar, L. Vieira, F. Veloso, A.	2016	Portugal	Kinetic analysis of GAIT in the second and third trimesters of pregnancy	Journal of Mechanics in Medicine and Biology	21
Sunaga, Y. Kanemura, N. Anan, M. Takahashi, M. Shinkoda, K.	2016	Japan	Estimation of inertial parameters of the lower trunk in pregnant Japanese women: A longitudinal comparative study and application to motion analysis	Appl Ergon	22
Forczek, W. Masłoń, A. Frączek, B. Curyło, M. Salamaga, M. Suder, A.	2019	United States	Does the first trimester of pregnancy induce alterations in the walking pattern?	PLos ONE	23

# Investigated periods

As shown in Table 3, these studies investigated different trimesters of pregnancy. Two studies [15, 23] surveyed women from the prepregnancy to pregnancy periods, and one study [15] involved the postpartum period. During pregnancy, the two studies selected different stages. The former15 studied the end stage of pregnancy, while the latter [23] studied the first trimester. Other studies included non-pregnant women as the control group. Three studies [10, 12, 17]

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Articles	Target population and Age (years)	Time of the study	Sample size		
10	Pregnant :28-40 Non-pregnant :21-35	Pregnant: ≤ 16 weeks; 24 weeks; 32 weeks; and 38 weeks of gestation; and 8 weeks postpartum Non-pregnant: tested beginning; 16 weeks later; and 32 weeks later.	Non-pregnant: 12		
11	Pregnant: 32.8 ± 5 Non-pregnant:31.1 ± 6	Pregnant: 11 to 14 weeks for the first trimester; 19 to 22 weeks for the second trimester; and 36 to 39 weeks for the third trimester of gestation; and 6 to 8 weeks postpartum. Non-pregnant: just once, but not mentioned the time	Pregnant:12; non-pregnant:12		
12	Pregnant: 31 ± 4 Non-pregnant: 31 ± 4	Pregnant:4-week intervals during the regnant period;6 weeks,12 weeks,6 months postpartum (46 weeks,52 weeks, and 64 weeks) Non-pregnant:4-week intervals for 40 weeks; 6 weeks,12 weeks, and 6 months after the 40 <sup>th</sup> week (46 weeks,52 weeks, and 64 weeks)	Pregnant:15; Non-pregnant:15		
13	Pregnant: 29.5 ± 4.9 Non-pregnant: 26.5 ± 6.4	Pregnant: Average 20.9 ± 1.2 weeks of gestation Average 35.8 ± 1.5 weeks of gestation Non-pregnant: single study visit, but time is not sure.	Pregnant:41; Non-pregnant:40		
14	Pregnant(non-fallers): 30.6 ± 3.8 Pregnant(fallers): 29.4 ± 4.7 Non-pregnant: 26.5 ± 6.4	Pregnant: average 20.9 ± 1.2 weeks of gestation; average 35.8 ± 1.5 weeks of gestation Non-pregnant: single study visit, time is not sure, dates were collected in the week following menses.	f Pregnant:41; Non-pregnant:40		
15	29.15 ± 3.5	Before pregnancy (pre-pregnancy state); 33-average week of gestation (in pregnancy state); A half-year after delivery (post-pregnancy state).	13(from Non-pregnant to Pregnant)		
16	Pregnant:32.5 ± 2.6 Non-pregnant: 20.58 ± 1.73	Pregnant: Later stage of the second trimester (2T); Third trimester (3T). Non-pregnant: Just once, but time is not sure	Pregnant:22; Non-pregnant:12		
17	Pregnant:32.6 ± 4.3 Non-pregnant: 28.9 ± 4.1	Pregnant:18 weeks or less of gestation;24 weeks of gestation; 32 weeks of gestation;38 weeks of gestation; 8 weeks post-birth. Non-pregnant: Tested beginning; 16 weeks later; 32 weeks later.	Pregnant:9; Non-pregnant:12		
18	Pregnant: 32.29 ± 4.62 Non-pregnant: 27.42 ± 3.13	Pregnant: 14-26 weeks of gestation; 27-40 weeks of gestation; 12 weeks postpartum. Nonpregnant: Once, but time is not mentioned	Pregnant:13; Non-pregnant:20		
19	Pregnant: 27.3 ± 1.3 Non-pregnant: 26.9 ± 1.4	Pregnant: 27.3 ± 1.3 Pregnant: 9.7 ± 1.3 weeks of gestation(average); 20.9 ± 2.3 weeks of			
20	Pregnant: 28.3 ± 3.4 Non-pregnant: 21.3 ± 0.9	Pregnant: 35.1 ± 1.4 weeks of gestation (mean gestation), third trimester (specific time was not mentioned). Non-pregnant: when pregnant women in the 35.1 ± 1.4 weeks of the gestation	Pregnant:8; Non-pregnant:8		
21	Pregnant:32.4 ± 2.6 Non-pregnant: 20.58 ± 1.73	Pregnant: 27.1 ± 1.3 weeks of gestation; 36.4±1.0 weeks of gestation Non pregnant: once, but time was not mentioned	Pregnant:24; Non-pregnant:12		
22	Pregnant: 34.4 ± 5.9 Non-pregnant:29.3 ± 2.4	Pregnant: 16 <sup>th</sup> -18 <sup>th</sup> weeks of gestation (Exam 1); 24 <sup>th</sup> -25 <sup>th</sup> weeks of gestation (Exam 2); and 32 <sup>nd</sup> -33 <sup>rd</sup> weeks of gestation (Exam 3) Nonpregnant: once, time was not mentioned	Pregnant:8; Non-pregnant:7		
23	30.2 ± 3.05	Before pregnancy; 12 <sup>th</sup> week of gestation.	35 Non-pregnant subjects i the first experimental session 15 subjects become pregnation		

Table 3: Publications: Characteristics of the papers on the locomotion of women throughout pregnancy.

performed repeated measurements in the control group; the other studies were only conducted once. In total, six articles [10-12, 15, 17, 18] covered the postpartum period.

## Sample size

The largest sample size was 81, of which 41 were pregnant and 40 were non-pregnant [13, 14]. The second largest was 72, of which 36 were pregnant and 36 were nonpregnant [19]. The smallest sample size was 15, of which 8 were pregnant and 7 were non-pregnant [22]. The second-lowest was 16, of which 8 were pregnant and 8 were non-pregnant [20]. The rest of the research sample sizes were between 21 and 36 (4 of 20+, 5 of 30+)

# Objectives

The objectives of this study are presented in Table 4. The main concept of the research was to determine the biomechanical changes in pre-, in-, and post-pregnancy periods. All studies focused on kinematic or kinetic changes in pregnancy compared with non-pregnancy.

Among them, six studies focused on balance and stability [11-14, 19, 20]: one study explored the changes in balance during pregnancy

[11]; one investigated the stance width of pregnant women during pregnancy and postpartum periods [12]; one estimated the dynamic postural stability in mid and late pregnant group and non-pregnant control group [13]; one study compared dynamic postural stability among pregnant fallers, pregnant non-fallers, and non-pregnant women [14] and also explored the static balance and fall rate changes during pregnancy [11] as well as the monthly rate of falls [12] and whether regular exercise during pregnancy was related to the incidence of falls [14] one investigated the characteristics of the Center Of Pressure (COP) progression during pregnancy and regionalized COP progression characteristics of pregnant women at different gestational stages [19] one study analyzed balance strategies during pregnancy from a kinematic perspective [20]. Five studies were conducted on the biomechanics of the trunk [10, 17, 18, 22, 23]. Estimations of these studies include: pregnant related kinematic changes of the trunk segment and changes in mediolateral width in the supporting basement by testing five tasks (seated and standing forward flexion, left-right flexion, seated-sitting axial rotation) [10]; changes in the thoracic spine during pregnancy and postpartum, and the movement between the thoracic and lumbar spines in comparison with nonpregnant women [17]; inspection of the causes of low back pain during pregnancy, and

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	Table 4: Objectives of the studies.									
Articles	Objectives									
10	To investigate the effects of pregnancy on the kinematics of trunk segments during seating and standing forward flexion, side-to-side flexion, and axis rotation when seating. The effect of pregnancy on the mediolateral width of the support base adopted for these tasks was also investigated.									
11	To determine whether body balance changes during pregnancy and to check whether the rate of falls increases.									
12	To track balance and stance width in pregnant women throughout the pregnancy and postpartum periods. To track monthly incidences of falls.									
13	To investigate pregnant dynamic postural stability of pregnant women in the second and third trimesters by comparing with non-pregnant women.									
14	To compare dynamic postural stability among pregnant women fallers, pregnant non-fallers, and non-pregnant women. To test whether regular exercise has a relationship with pregnancy fall.									
15	Primary purpose: to measure the selected gait parameters and evaluate the differences in their way of locomotion in one group of women before pregnancy, during pregnancy, and after delivery. Further purpose: to determine the effect of gestation on the biomechanical walking pattern and determine whether a 6-month period after delivery is sufficient to reach the pre-pregnancy gait pattern.									
16	To quantify the pregnant lower limb kinematics variables during gait of pregnant women in second and third trimesters on spatial and temporal parameters compared to that with the nonpregnant group.									
17	To determine the systematic changes in the movement range of pelvic and spine thoracic segments, movement between the thoracolumbar spine, and spatiotemporal characteristics of step width, stride length, and speed during walking during pregnancy and early period postpartum.									
18	To investigate the causes of low back pain during pregnancy and explore the potential of using the spine and surface topography system to accurat measure spinal posture and pelvic position during pregnancy without any harmful radiation.									
19	To explore the characteristics of the progression of the Center of Pressure (COP) during pregnancy. To investigate regionalized COP progression characteristics of pregnant women at different gestational stages during normal walking.									
20	To clearly explain the changes in balance strategies during pregnancy from a kinematic perspective.									
21	To quantify the lower limb dynamics of gait and to compare it between women in mid and late pregnancy and the non-pregnant group									
22	To quantify the inertial parameters of the lower trunk segment. To compare the kinetic data during the task calculated. To estimate Japanese pregnant women's Body Segment Inertial Parameters (BSPs) and quantify the change in BSPs over time. Kinetic analysis or pregnant women when they are performing motor tasks.									
23	To perform pregnant gait kinematic analysis related to fetal development in the first trimester of pregnancy in the locomotor system.									

measuring the spinal posture and pelvic position during pregnancy [18]; and Japanese pregnant Body Segment Interstitial Parameters (BSPs) and variations in BSPs over time. The lower trunk segment moment, COM location, and COM velocity of pregnant women when performing motor tasks were studied based on the estimated BSPs. The motor tasks included standing up from a chair, picking up a square tray, turning to the right, walking a few steps, turning toward the destination, performing targeted movements when standing up from a chair or walking [22] and the biomechanical changes of the pelvis in the first trimester [23].

Five studies conducted gait analysis [15-17, 21, 23] investigation of gait parameters in one group of three different states (before pregnancy, during pregnancy, and after delivery [15]); quantification and comparison of the lower limb kinematics and spatial/temporal parameters of gait between pregnancy (in the second and third trimesters) and non-pregnancy [16]; study on temporal-spatial characteristics of step width, stride length, and speed as pregnancy progresses, in early postnatal period and compared with non-pregnant [17]; quantification and comparison of lower limb kinetics of gait between women in mid and late pregnancy and non-pregnancy groups [21] and analysis of kinematic changes in the locomotor system associated with fetal development in the first trimester of pregnancy [23].

# Parameters

Fourteen articles focused on different biomechanical parameters. Their results are described in Table 5. Six articles studied balance and stability using the parameter COP [11-14, 19, 20]: the path length and Average Radial Displacement (ARD) of the COP when eyes are opened and closed [11]; traditional parameters about the COP, including standard deviation of the displacement about the mean and mean sway velocity in the Anterior Posterior (AP), Medial Lateral (ML), and

Combined Radial (RAD) directions; 95% power frequency in the AP and RAD directions, and Angular Deviation (Ang Dev) of the principal sway direction from the AP axis [12]. Reaction time and the movement of the COP (reaction time, initial sway, total sway, and sway velocity) [13, 14]. COP parameters, including maximum Velocity ( $V_{max}$ ), Average Velocity ( $V_{ave}$ ), Duration (DCOP), ML and AP displacements in each region [19]; the anterior COP displacement at the maximum Functional Reach Test (FRT) distance, and FRT is a static balance test [20].

Five studies investigated the biomechanics of the trunk [10, 17, 18, 22, 23]: angular motion of the thoracic and pelvic segments, and the relative rotation between the two segments during forward flexion activities (seated and standing), side-to-side flexion (seated and standing), and axial rotation (seated) [10]; the trunk kinematic cluster, which included the range of motion of the thoracic and pelvic segments, and the thoracolumbar spine in the sagittal, coronal, and transverse planes [17]; anthropometric data of the whole body, including the trunk segment, such as age (years), height (cm), initial weight (kg), weight gain (kg), abdominal circumference (cm), and completed back pain assessment and disability questionnaires [18]; Body Segment Inertial Parameters (BSPs); motion analysis [22]; and position of the pelvis and mean width of the Base of Support (BOS) in the double support phase [23].

Five studies conducted gait analysis [15-17, 21, 23]: gait characteristics, including Velocity (v), Gait Frequency (f), Length of Steps (l), Time of Single (SS) and Double Supports (DS), width of the BOS in double support phase, and ranges of motion of the lower limb joints, including the ankle, knee, and hip [15]; kinematic and kinetic parameters, including angular displacement and range of motion of the ankle, knee, and hip joints, walking speed, double limb support time, time of support and flight phases of both lower limbs, stride width,

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Articlas	Parameters
Articles 10	Segment angular motion
	Relative rotation between the thoracic and pelvic segments
11	Path length and Average radial displacement of the center of pressure (eyes open and eyes closed)
12	Center of Pressure (COP) movement COP parameters: Standard Deviation of the displacement about the mean (St. Dev) and mean sway velocity (Vel) in the in the Anterior-Posterior (AP), Medial–Lateral (ML),and Combined Radial (RAD) directions; 95% power frequency in the AP and RAD directions; and angular deviation (AngDev) of the principal sway direction from the AP axis. Perceived sense of balance Preferred stance width Numbers of fall incidences The outcome of the laboratory-based balance measures
13	Reaction time Center of Pressure (COP) movement (reaction time, initial sway, total sway, and sway velocity).
14	Medical file Self-reported pre-pregnancy mass Data about the daily activities, exercise participation, and fall history. Postural reaction time and Center Of Pressure (COP) movement data, in response to translational perturbations, Reaction time, initial sway, total sway, and sway velocity.
15	Pre-, in-, and post-pregnancy Women's locomotion at a natural speed Inter-Asis: distance between Anterior Superior Iliac Spines; Body mass Gait characteristics: velocity (v), gait frequency (f), the length of steps (I), and time of a single (SS) and Double Support (DS). Ranges of motion in the sagittal plane in the major joints of the lower limbs: ankle, knee, and hip, and calculated the width of the Base of Support (BOS in the double support phase of gait.
16	Angular displacement in ankle, knee, and hip in degree The range of motion of each joint Kinematic and kinetic parameters Walking speed; cycle time; right- and left-step time; double limb support time; time of support and flight phases in both lower limbs; stride width; stride length; right- and left-step length; joint angles in the sagittal plane, frontal plane, transverse plane and transverse plane of the hip, knee, and ankle for right and left lower limbs
17	velocity, stride length, and step width The trunk kinematic cluster included a range of motion for the thoracic and pelvic segments and the thoracolumbar spine in the sagittal, coronal, and transverse planes.
18	Anthropometric data Age (years) Height (cm) Initial weight (kg) Weight gain (kg) Abdominal circumference (cm) Back pain : Visual Analogue Pain Scale (VAS) Oswestry low back Disability Questionnaire (ODQ) German version of the Roland-Morris disability questionnaire
19	COP Maximum Velocity (V <sub>max</sub> ), Average Velocity (V <sub>ave</sub> ), Duration (D <sub>COP</sub> ), medial-lateral displacement in each region. Original COP medial-lateral and anterior-posterior displacement and duration during the whole stance phase were computed through the Pedar-x software package. (COP velocity was calculated as COP resultant displacement divided by the corresponding time it passed).
20	Age@height, weight The kinematics of the balance strategy. Performance of the Functional Reach Test (FRT). The maximum FRT distance (FRT max): the leg joint moments (hip, knee, and ankle), the Ground Reaction Force (GRF) of the legs (vertical and anterior), the anterior Center of Pressure (COP) displacement, and the leg and trunk angles in the sagittal plane.
21	kinetic pattern curves (the three components of the GRF normalized to units of body weight (BW)) The net joint moments and powers of the ankle, knee, and hip
22	Body Segment Inertial Parameters (BSPs) Motion analysis
23	Anthropometric measurements. Gait registration. Assessment of the feet loading pattern.

stride length, right and left step length cycle time16; kinetic parameters, including the three components of the Ground Reaction Force (GRF) normalized to units of body weight, net joint moments, and powers of the ankle, knee, and hip joints [21]; anthropometric measurements, gait registration, and assessment of the feet load pattern23; velocity, stride length, and step width [17].

# **Measurement Tools**

Table 6 summarizes the measurement tools used in the 14 studies. The most frequently adopted tool is force plates [11-14, 16, 17, 21-

23] followed by motion analysis systems, including an expert vision motion analysis system [10, 17] Vicon [15, 20, 22] Visual 3D Software (C-Motion Inc., Germantown, USA), [16, 23] and Qualisys Track Manager [21]. In one of the study, researchers used a radiation-free spine and surface topography system (Formetric, Diers International GmbH, Germany) to measure spinal posture and pelvic position [18]. In another study, spatiotemporal parameters were measured based on electrodes attached to the novel Pedar insole plantar pressure measurement system (Novel GmbH, Munich, Germany) [19]. Two studies used questionnaires: self-evaluation questionnaire-perceived

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Articles	Measurement tools								
10	Expert Vision Motion Analysis System (Eva HiRes 5.00, Motion Analysis Corporation, Santa Rosa, California, USA) Eight 8 mm video cameras A height-adjustable chair Kintrak version 5.7 (Motion Analysis Corporation)								
11	Stable force platform (50 × 50 cm; model 9284; Kistler Instrument Corp, Amherst, NY)								
12	Self-evaluation questionnaire: the perceived sense of balance Track fall incidences (five categories) Force plate (model BP600900, AMTI, Watertown, MA)								
3	Equitest posture platform under the Motor Control Test (MCT) protocol (Neurocom, Int., Clackamas, OR) Underfoot force plates								
14	Force plate Equitest posture platform under the Motor Control Test (MCT) protocol (NeuroCom International, Inc., Clackamas, OR, USA)								
15	Vicon 250 (Oxford Metrics Limited, Oxford, England)								
16	Visual 3D software (C-Motion Inc., Germantown, USA) Ten high-speed infrared cameras (Oqus-300, Qualisys, Sweden), rate: 200 Hz Software Qualisys Track Manager (QTM; Qualisys AB, Gothenburg, Sweden) Two Kistler force platforms (Kistler AG, Winterthur, Switzerland, length: 0.60 m, width: 0.40m), rate: 1000 Hz. Butterworth digital lowpass filter, at 10 Hz cutoff frequency								
17	Eight camera motion analysis system A Motion Analysis Corporation™ Expert Vision System™ a together with eight synchronized cameras (NEC T1-23A) Kistler™ 9281 force platform (sampling at 960Hz) EVa HiRes™ version 4.0 (Motion Analysis Corporation™)								
18	A radiation-free spine and surface topography system (Formetric, Diers International GmbH, Germany). Roland-Morris disability questionnaire (German version) Oswestry Low Back Disability Questionnaire (ODQ) Visual Analogue Pain Scale (VAS).								
19	The Novel Pedar insole plantar pressure measurement system (Novel GmbH, Munich, Germany)								
20	Vicon Nexus 3D motion analysis system (Vicon Peak Oxford, UK) Force plates (AMTI MA, USA) Ten infrared cameras (sampling frequency: 120 Hz) Functional reach test								
21	A three-dimensional (3D) kinetic analysis Ten high-speed infrared cameras (Oqus-300, Qualisys, Sweden), rate:200 Hz. Kistler platforms (Kistler AG, Winterthur, Switzerland) One AMTI platform (Advanced Mechanical Technology, Inc., Watertown). The capture hardware The Qualisys USB Analog Qualisys Track Manager (QTM; Qualisys ABr, Gothenburg, Sweden) software. Both data sequences were recorded in the same file.								
22	Eight infrared cameras (Vicon Motion Systems, Oxford, UK) Motion analysis software Vicon NEXUS 1.7.1. (Vicon Motion Systems, Oxford, UK) Two piled square plates (weight, 8.8 N; depth, 20 cm; width, 30 cm; height, 4 cm) Four force plates (Kistler, Winterthur, Switzerland) Body Builder software (Vicon Motion Systems, Oxford, UK)								
23	Frankfurt plane Stadiometer Clinical balance scale Harpenden Skinfold caliper Five video cameras A 3D motion analysis system (Vicon 250; Oxford Metrics Limited, Oxford, United Kingdom) FreeMED force platform (Sensor Medica, Italy)								

sense of balance, track fall incidences (five categories) [12] the German version of the Roland-Morris disability questionnaire, and the Oswestry Low Back Disability Questionnaire (ODQ). The level of back pain was measured using a Visual Analog Scale (VAS) [18]. Some studies used clinical tests, such as the Motor Control Test (MCT) [13, 14] functional reach test [20] and clinical balance scale [23]. Other tools have also been used to assist investigations, such as a height-adjustable chair [10]. Butterworth digital low-pass filter [16] Frankfurt plane, Stadiometer, Harpenden, and Skinfold caliper (Table 6) [23].

## Outcomes

Because the investigated periods in these studies were inconsistent, the study results related to the review purpose from those 14 studies could not be classified according to time. Instead, they were analyzed according to the research goals. The results of these 14 studies are summarized in Table 7.

# Balance and stability changes during pre-, in-, and post-pregnancy

Pregnancy affects balance and stability. Postural balance changes were indicated by stance width, COP, perceived sense of balance, and sway [11-14]. Postural stability was maintained in the first trimester, reduced as the pregnancy progressed, and did not recover at 6 to 8 weeks postpartum [11]. In the first trimester, the path length of the COP of pregnancies in eyes closed/opened and the ARD of the COP of

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Articles	Results										
10	Pregnancy impacts the trunk movement when standing and sitting.										
11	Pregnancy impacts the body's balance, the body's perception of balance, and fall rate.										
12	Pregnancy impacts the perceived balance, stance width, and falling rate of the pregnant woman.										
13	The study on the pregnant women in their second and third trimesters, and the non-pregnant control women on the perturbation reaction time, initial sway, total sway, and sway velocity, revealed that dynamic postural stability changes during the pregnancy period.										
14	Compared with the fall rate, parameters, such as initial sway response, total sway, sway velocity, and response time, were different among those three groups (i.e., pregnancy fallers, pregnant non-fallers, and non-pregnant,). In addition, exercise influenced the pregnancy's falling rate.										
15	The aspects of gait, including the mean joint ranges of the ankle, knee, and hip, were not changed during the pregnancy period. The velocity and frequency of steps, average length of steps, duration of double support and single support during free gait, and average value of the support area width of gravid women were changed.										
16	The following parameters were not be significantly influenced by the pregnancy: velocity, stride width, right-/left-step time, cycle time, and support time, and phases of flight. The following parameters were influenced by the pregnancy: stride length, right/left stride length, double limb support time, and joint kinematics (hip, knee, ankle).										
17	Pregnancy impacted the stride length, step length, lateral range of motion of the pelvic segments and thoracolumbar spine, and the movement of the pelvic part in the coronal plane.										
18	During pregnancy, the thoracic kyphosis increased but lumbar anterior kyphosis did not improve. Lateral deviation of the spine was remarkably decreased. The position of the pelvis showed no remarkable change during and after pregnancy.										
19	The COP was different because of pregnancy.										
20	The following aspects were influenced by pregnancy: the outcome of the functional reach test (FRT), bilateral hip extension, bilateral ankle plantar flexion moments, right ankle plantarflexion moment, and balance strategy.										
21	Between the second and third trimesters: Most pregnant women's GRF pattern during gait remained unchanged, but decreased for the left stance vertical GRF and the third peak of GRF. Pregnant women were compared with nonpregnant groups: from the lateral to the medial direction, AP GRF, joint moments, the ankle and hip joint movement in planes (sagittal plane, frontal plane, and transverse plane), and joint power peak were different.										
22	Pregnancy impacted the absolute and relative masses of the lower trunk segment, which increased as pregnancy progressed.										
23	Pregnancy does not influence the gait pattern in spatiotemporal parameters, the shape of the medial longitudinal arch, the plantar pressure during gait the first trimester Pregnancy influences the way they place feet on the ground, as well as the ankle separation width and angular changes in the coronal plane. For the movement of the pelvis, the width dimension and motion range in sagittal and coronal planes did not change; however, pelvic rotations in the transverse plane as well as pelvic obliguity and rotation were changed.										

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Summary Quality
10	Yes	No	NR	No	NR	Yes	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	7(i)
11	Yes	No	No	No	No	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	6(i)
12	Yes	NO	NR	No	NR	Yes	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	7(i)
13	Yes	Yes	Yes	No	NR	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	8(i)
14	Yes	Yes	Yes	No	NR	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	8(i)
15	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	10(i)
16	Yes	Yes	NR	No	No	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	7(i)
17	Yes	NR	NR	NR	NR	Yes	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	7(i)
18	No	No	No	NR	NR	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	5(i)
19	Yes	No	No	No	No	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	6(i)
20	Yes	No	No	NR	NR	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	6(i)
21	Yes	No	NR	No	NR	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	6(i)
22	Yes	No	No	No	No	No	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	6(i)
23	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NA	NA	Yes	NR	Yes	Yes	10(i)

Table 8: Assessments of the 14 reviewed Studies using the quality assessment tool.

pregnancies in eyes opened were not significantly different from those in the non-pregnant group; however, there was a significant difference in the ARD of the COP when eyes were closed, which indicated that in the first trimester, the pregnant balance was not significantly different from that in the non-pregnant [11]. The same parameter values in the second trimester, third trimester, and 6 to 8 weeks postpartum were significantly higher than those in non-pregnant women, indicating a balance decrease in those three periods [11] This indicates that pregnant women have an increasing need for visual cues to maintain balance [11]. 6-month postpartum, compared with an age-matched non-pregnant control group and found that the Sense of Balance (SB), which was the self-assessment balance ability. It was found that the higher the score was, the more unstable the subject became; specifically, it increased from 16<sup>th</sup> week of pregnancy to 6 weeks after delivery, and then decreased. Six months after delivery, the value of the SB decreased to the lowest; however, it was still higher than that in the non-pregnant group.12 During pregnancy, postural sway in the AP and radial directions increases, while after delivery it decreased.12 ML sway remained unchanged during pregnancy, but increased after delivery [12]. The preferred Stance Width (SW) was found to increase

A study12 was conducted on a cohort of 16 weeks gestation to

during pregnancy (from weeks 16 to 40) and drop to control levels after delivery, indicating decreased balance during pregnancy and increased balance in the postpartum period [12].

The response time to perturbation did not change during pregnancy [13] and also did not significantly differ between pregnant fallers, pregnant non-fallers, and non-pregnant women [14] however, the movement of the COP, in terms of initial sway, sway velocity, and total sway, changed remarkably [13-14]. From the non-pregnancy period to the second trimester, the initial sway remained stable without perturbations, but was reduced in the third trimester [13] and pregnant fallers had significantly less initial sway than pregnant non-fallers and non-pregnant women [14]. The amplitude of the initial sway increased with the level of perturbations, and backward perturbations resulted in larger amplitudes than forwarding perturbations [13-14]. Without perturbation, sway velocity was the lowest in the third trimester. It increased with the perturbation level, and forward perturbations resulted in a more remarkable sway velocity than backward perturbations. The third trimester showed less total sway than the second trimester in the control group. Forward perturbations elicited more total sway than backward perturbations. Large perturbations produced more total sway than medium and small perturbations [13, 14]. Pregnant fallers had significantly less sway velocity and total sway than other two groups +. There was no difference in these aspects between the pregnant non-fallers and non-pregnant groups [14].

Balance strategies changed during pregnancy. Pregnant women in their second and third trimesters were found to rely more on the ankle joint strategy than the non-pregnant, and with the progression of pregnancy, the ankle joint contributed more to balance maintenance; however, analysis of the first trimester and postpartum periods were not included [20].

The characteristics of the COP also changed depending on the change in pregnancy to maintain balance [19] pregnant women had a visibly lateral shift of the COP displacement, slower COP  $V_{\rm ave}$  in the hindfoot and midfoot, faster COP  $V_{\rm ave}$  in the forefoot,  $V_{\rm max}$  over all regions decreased as the pregnancy progressed, COP moved forward with slower velocity over the rearfoot and midfoot, and faster over the forefoot as the pregnancy progressed.

#### Changes of the trunk motion pre-, in-, and post-pregnancy

The motion of the trunk was influenced by pregnancy. No difference was found in the displacement of the thoracic or pelvic segment or the range of motion of the thoracolumbar spine during early gestation [10]. The pelvic width and range of motion of the pelvis in the sagittal and coronal planes did not change significantly from prepregnancy to the 12th-16th pregnancy week; only the lateral plane pelvic rotation was significantly reduced [23]. As pregnancy progressed, the influence on the motion of thoracic or pelvic segment or the range of motion for the thoracolumbar spine and support width were varied during seated and standing trunk forward flexion, trunk side-to-side flexion, and trunk axial rotation [10]. Thoracic segment displacement decreased during trunk forward flexion and trunk axial rotation; pelvic segment displacement decreased significantly at the late gestation in seat forward flexion, but not during trunk axial rotation, and had no difference in standing forward flexion. Thoracolumbar spine range of motion decreased as pregnancy progressed during trunk axial rotation. However, it did not significantly differ during seated forward flexion and was less during standing forward flexion. The base of support was not significantly affected as pregnancy progressed during trunk axial rotation, but was significantly greater than non-pregnant when standing during side-to-side flexion and forward flexion. There was no significant difference for motion of thoracic or pelvic segment or the range of motion for the thoracolumbar spine doing seated and standing side-to-side flexion. Another study [17] showed that, as pregnancy progresses, the range of motion of the pelvic segment and thoracolumbar spine declined significantly in the rotation around the vertical axis. Further, the range of motion of the pelvic part around the antero posterior axis (lateral tilt) also showed a significant decrease.

In addition to trunk motion, the shape of the trunk was found to be influenced. One reviewed article 18 indicated that thoracic lordosis increased during pregnancy, whereas no increase was found in lumbar lordosis. The lateral deviation decreased during the second trimester, third trimester, and postpartum period [18]. No significant change was found in the position of the pelvis during and after pregnancy; however, the pelvic tilt increased as pregnancy progressed, and once after delivery (postpartum-12 weeks after delivery) [18].

After delivery, the thoracic or pelvic segment or the range of motion for the thoracolumbar spine and support width showed no significant difference between seated and standing trunk forward flexion, trunk side-to-side flexion, and trunk axial rotation as pregnant [10]. After delivery, the range of motion of the pelvis was smaller, while the thoracic region had a larger range of motion than in late pregnancy [17]. For postpartum to 12 weeks after delivery, lateral deviation and pelvic tilt did not recover [18].

Pregnancy influenced the body mass, segment COM location, trunk segment moment of inertia, and lower trunk length of the women [22]. There was no remarkable difference on absolute and relative lower trunk masses with pregnancy between the 16th and 18th weeks compared to non-pregnant women. As pregnancy progressed, 24th-25th and  $32^{nd}$ - $33^{rd}$  pregnancy weeks, the absolute and relative lower trunk masses of the maternal group were significantly greater than those of the non-pregnant control group. The body mass, height of the uterine fundus, and abdominal girth increased significantly from 16th-18th to 32<sup>nd</sup>-33<sup>rd</sup> pregnancy weeks. The positions of segments COM were more anterior in the pregnant group than in the nonpregnant group, while they showed no significant difference in superior-inferior and the ML directions. Heavier segment mass and smaller radius of gyration in 16th-18th and 32nd-33rd pregnancy weeks owing to the longer segment length in pregnancies, than non-pregnant group were found. The lower trunk segment moment of inertia in the anterio-posterior direction in the 32<sup>nd</sup>-33<sup>rd</sup> pregnancy weeks was larger than that of the non-pregnant women. The length of the lower trunk segment slightly reduced as the pregnancy progressed, which may be caused by the increased spinal curvature.

#### Gait changes during pre-, in-, and post-pregnancy

Pregnant influenced some aspects of the women's gait. No significant changes were found in the average ranges of motion of the ankle, knee, and hip joints in the sagittal plane before, during, and after pregnancy [15]. However, another study indicated that, compared with the non-pregnant group, the extension and adduction of the right hip during the stance phase between the second and third trimesters decreased [16]. The maximum extension and abduction of the right thigh, maximum flexion of the left knee, and maximum plantar flexion of the right ankle of pregnant women between the second and third trimesters showed remarkable differences [16]. Most pregnant subjects experience an increase in left knee flexion and a decrease in right ankle plantar flexion [16].

The results of the reviewed studies were not the same in terms of

spatial and temporal parameters.

In the first trimester, the basic kinematic gait parameters did not change significantly [23]. There was a significant decrease in the length of the right and left steps; therefore, a significant reduction in the stride length was found in the non-pregnant group, as well as in the second trimester and third trimester of pregnancy [16] One reviewed study17 indicated that this decreased trend was linear.

No significant changes in walking speed, stride width, right and left step time, cycle time, time of support, and flight phases were found during the non-pregnant stage and second and third trimesters [16]. However, one study indicated that the strip width has an increasing linear trend as pregnancy progressed [17] and another reviewed study [15] showed that v significantly decreases from pre-pregnancy to pregnancy and increases significantly after pregnancy. The f had the same change pattern, and the value of v and f returned to the prepregnancy state at 6 months postpartum. No significant difference was found in the l between the pre- and post-pregnancy periods, although it was significantly lower during pregnancy [15]. The duration of DS increased as pregnancy progressed, and was significantly longer than that before and after pregnancy [15]. The BOS in the pregnancy period was higher than that before and after pregnancy, and returned to the same level as that before pregnancy [15]. After birth, the stride was readapted [17]

The change patterns of the Ground Reaction Force (GRF) in the second and third trimesters were almost the same, but the values were different [21]. In the left stance, the last peak of the vertical GRF showed a significant decrease, which was approximately 5% of BW [21]. Compared with that in the pre-pregnancy period, the ML GRFs showed remarkable differences in the second and third trimesters [21].

Pregnancy impacts the joint moments, muscle participation patterns, and joint power [21]. Most muscle participation patterns changed at the end of the stance phase, and asymmetry may occur between two lower limbs. The second peak of the right hip joint moment in the sagittal plane significantly decreased in those pregnant in second and third trimesters compared with those in the nonpregnant group, indicating a reduction participation of hip flexors. This peak value showed significant difference between the left and right hips in the third trimester, implicating an asymmetric muscle participation pattern. Increased involvement of the external rotator muscle in the second trimester of pregnancy was observed at the first peak of the left hip moment. The participation of the knee extensor muscles decreased, and the knee flexor muscle increased during the second trimester of pregnancy compared to that during the pre-pregnancy period. Ankle dorsiflexor participation decreased during the second and third trimesters compared to that during the pre-pregnancy period. A significant decrease in the involvement of the lateral malleolus muscle, associated with the first peak of left ankle moment in the frontal plane, was observed during the second trimester of pregnancy. In the final stages of the stance phase, joint production and mechanical energy absorption in the lower limbs decreased during pregnancy, compared to that of the non-pregnant group. Meanwhile, no significant difference of the joint power of the hip, knee, and ankle in the three anatomic planes of pregnant women in the second trimester compared with those in nonpregnant and in the third trimester.

# **Quality Assessment**

A quality assessment was conducted using the NHLBI Quality Assessment Tool for Observational Cohort and Cross-sectional Studies.26,27 For 0-4 "yes" from 14 questions in the assessment tool, a study will be graded as "poor Quality," while 5-10 "yes" means "fair Quality" and 11-14 "yes" means "Good Quality."

Table 8 shows the quality of the 14 studies. All studies were fair (5-10), and the mean score was 7.071/14. The table also lists assessments of the 14 reviewed studies using the quality assessment tool

All the authors have fully described their study goals. Nine authors did not clearly specify and define their study participants, such as describing their demographics and location of the study participants [10-12, 17-22]. Only four studies [13-15, 23] can fully represent the target population because they had at least 50% eligible persons attended the research, while the sample size of the rest of the research may have caused the research to be biased. Only two [15, 23] studies have formulated inclusion and exclusion criteria, and used the same essential criteria for all subjects involved. No study explained the reason for the sample size, and did not discuss statistical power. This was not a "fatal flaw," although none of these studies mentioned any information about efficacy or sample size, as observational cohort studies can be exploratory studies that usually do not provide information about strength or sample size [26]. This indicates that the authors did not consider whether the sample size was sufficient to answer the prespecified question. Only five studies [10, 12, 15, 17, 23] can confirm that pregnancy state existed before the possible body's biomechanical changes, and they provided evidence for the causal relationship between pregnancy and possible biomechanical changes in the body, because the control group performed several tests as experimental groups [10, 12, 15, 17] or studied the pre-pregnancy statement of the same pregnant group [23] while control groups from other studies were only tested once.

All studies had sufficient time to observe the impact of pregnancy on human biomechanics, because pregnancy time was regarded as the exposure level, time was the only measurement, and Q9 and Q10 were not applicable. None of the studies mentioned the use of blinding.

# **Discussion and Conclusion**

During pregnancy, women experience substantial changes in physiology, morphology, and hormonal systems. These changes have profound effects on the biomechanics of the human body, particularly the musculoskeletal system, resulting in discomfort, pain, and decreased body stability. Sufficient biomechanical knowledge is critical for understanding the etiology and precautions of musculoskeletal disorders. With awareness of health problems in the pregnant cohort, identification, intervention, and precaution of problems have garnered attention. Studies have been conducted to determine the biomechanics of pregnancy. In addition, there have been review studies on summarization.

Because the pregnancy periods in these studies are inconsistent, further studies are required to determine which period is most biomechanically representative, and sample size should be determined according to certain statistical methods, which are not indicated in these studies. None of these 14 studies had such a large sample size to represent the universal pregnant population. The diversity of age, work, height, weight, and living habits makes it difficult to confirm a representative sample size. Although these studies provided valuable information, extended parameters that are necessary for a full understanding of pregnancy biomechanics can be further explored. For example, plantar pressure in the second and third trimesters and postpartum period [23] remains unclear.

Existing measurement methods are not comprehensive, such as

measuring waist circumference, which can only measure changes in the body circumference. However, they cannot measure body composition, muscle, fat, or inorganic modifications, and the ratio of these components affects the body's activities [25]. Selecting a better, and more specific evaluation method can improve the quality of research experiments. For example, adding body composition analysis, which can provide the weight distribution and composition of body segments. In addition, it provides clues to determine whether the increase in weight is owing to the fetus, fat, or muscle; the increased part is the limb or the abdomen [24]. Meanwhile, this measurement method cannot repeatedly measure exposure (pregnancy). Therefore, more comprehensive experiments involving pre-pregnant, in-pregnant, and post-pregnant individuals are required.

## **Contribution to Authorship**

Y.W., L.W., Y.P., Q.T. and M.Z. conceived the study. Y.W., L.W., Y.P., Q.T. and M.Z. provided plan. Y.W., L.W., Y.P., Q.T. and M.Z. carried out and analyzed. L.W. drafted the manuscript; all authors contributed to revisions and approved the final version.

#### **Details of Patient's Consent**

Not applicable

# **Details of Ethics Approval**

Not applicable

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#### **Conflicts of Interest**

The authors report no conflict of interest.

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