

RESEARCH ARTICLE

Adaptation of lung, chest wall, and respiratory muscles during pregnancy: preparing for birth

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Submitted 24 January 2019; accepted in final form 4 November 2019

LoMauro A, Aliverti A, Frykholm P, Alberico D, Persico N, Boschetti G, DeBellis M, Briganti F, Nosotti M, Righi I. Adaptation of lung, chest wall, and respiratory muscles during pregnancy: preparing for birth. *J Appl Physiol* 127: 1640–1650, 2019. First published November 7, 2019; doi:10.1152/jappphysiol.00035.2019.—A plethora of physiological and biochemical changes occur during normal pregnancy. The changes in the respiratory system have not been as well elucidated, in part because radioimaging is usually avoided during pregnancy. We aimed to use several noninvasive methods to characterize the adaptation of the respiratory system during the full course of pregnancy in preparation for childbirth. Eighteen otherwise healthy women (32.3 ± 2.8 yr) were recruited during early pregnancy. Spirometry, optoelectronic plethysmography, and ultrasonography were used to study changes in chest wall geometry, breathing pattern, lung and thoraco-abdominal volume variations, and diaphragmatic thickness in the first, second, and third trimesters. A group of nonpregnant women were used as control subjects. During the course of pregnancy, we observed a reorganization of rib cage geometry, in shape but not in volume. Despite the growing uterus, there was no lung restriction (forced vital capacity: $101 \pm 15\%$ predicted), but we did observe reduced rib cage expansion. Breathing frequency and diaphragmatic contribution to tidal volume and inspiratory capacity increased. Diaphragm thickness was maintained (1st trimester: 2.7 ± 0.8 mm, 3rd trimester: 2.5 ± 0.9 mm; $P = 0.187$), possibly indicating a conditioning effect to compensate for the effects of the growing uterus. We conclude that pregnancy preserved lung volumes, abdominal muscles, and the diaphragm at the expense of rib cage muscles.

NEW & NOTEWORTHY Noninvasive analysis of the kinematics of the chest wall and the diaphragm during resting conditions in pregnant women revealed significant changes in the pattern of thoracoabdominal breathing across the trimesters. That is, concomitant with the progressive changes of chest wall shape, the diaphragm increased its contribution to both spontaneous and maximal breathing, maintaining its thickness despite its lengthening due to the growing uterus. These results suggest that during pregnancy the diaphragm is conditioned to optimize its active role provided during parturition.

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diaphragm; optoelectronic plethysmography; position; pregnancy; ultrasound

INTRODUCTION

The physiology of pregnancy is characterized by hormonal, cardiovascular, respiratory, and muscular-skeletal changes that are associated with the modification of both the morphology and function of several organ systems (41a, 67). Both biochemical and mechanical pathways affect the anatomy and regulate the physiology of the respiratory system during normal pregnancy. The former includes increased levels of progesterone and relaxin, which induces collagen loss, with consequent relaxation of ligaments and cartilage (27, 52). An example of the latter is the growing uterus, with cranial shift of viscera as its principal mechanical effect (1). The combination of these factors progressively influences the geometry and the dimensions of the chest wall in terms of increasing subcostal angle as well as thoracic and abdominal perimeters (15, 16, 26, 41, 61).

The available literature is scant, outdated, or based on antiquated or invasive techniques, with conflicting results. Furthermore, most studies deal with one aspect only or exclusively consider the last trimester without following the progression of pregnancy. For example, lung volumes may be reported to be reduced or increased or to display no changes with gestation (16, 26, 28, 30, 33, 43, 47, 61, 67). The breathing pattern has been described as more thoracic (20, 26), although transdiaphragmatic pressure has not been shown to change at the end of pregnancy (16, 20). Such apparently conflicting results, i.e., similar diaphragmatic force but reduced abdominal expansion, can be a consequence of the method used. For instance, in one study the respective displacement of only one thoracic and one abdominal point was measured. Moreover, the authors considered only the seated position, which is normally characterized by predominantly thoracic breathing (55).

Several studies have found that maximal inspiratory and expiratory pressures, being global indexes of the forces developed by all the inspiratory and expiratory muscles, do not change with pregnancy (16, 26, 40). The capacity of the respiratory muscles to develop pressure therefore seems preserved, even though the geometry of the chest wall is signifi-

cantly affected during pregnancy. Abdominal muscles lengthen and change their muscle insertions while preserving force development (11, 25, 68). The diaphragm is shifted cranially at the end of pregnancy. This shift ranges from 1.5 to 4 cm, and it was quantified in the first half of the twentieth century by chest X-ray (44, 59, 61). Simultaneous changes in rib cage muscle function are less well elucidated.

The diaphragm has both ventilatory and nonventilatory (or expulsive) behaviors, including parturition. The former is accomplished by recruiting only fatigue-resistant (types S and FR) motor units, the latter by more fatigable motor units (types FIInt and FF). During ventilatory behavior the diaphragm develops ~10% of its total force-generating capacity (56), therefore having a large reserve of force generation and high levels of activation (21, 42). For these reasons, the diaphragm and the abdominal muscles are also important during the delivery stage, when they have to contract forcefully, acting as a brace and being the “engine” that expels the fetus (8–10, 18, 54, 57).

Some decades ago, maternity was prohibited for all women suffering from high-risk conditions. Recently, many institutions have changed their policies, and an increasing number of high-risk pregnancies are initiated and completed (17, 32, 34, 35, 46, 60, 66), leading to challenges that require a multidisciplinary medical approach. For this reason, increased knowledge of maternal physiological respiratory changes may help the physician to provide optimal care in these high-risk pregnancies. The present study represents a first step toward understanding the physiological adaptation of lung, chest wall, and respiratory muscles during normal pregnancy, also providing a base for future study of high-risk pregnancy.

The aim of this work was to characterize and progressively monitor changes of the respiratory system induced by pregnancy and to understand their mechanisms and possible implications. We therefore undertook a longitudinal multidimensional study to investigate different aspects of the respiratory function, using noninvasive and accurate techniques, at each trimester of pregnancy in a group of primiparous women.

The different aspects comprised chest wall geometry, breathing pattern, lung and thoracoabdominal volume variations, and diaphragmatic thickness and motion in seated and supine positions. In particular, we wanted to understand the net effect on the diaphragm of the progressively increased abdominal content, which may have two opposite effects: stretching and increased load.

MATERIALS AND METHODS

This is an observational, single-center, longitudinal, controlled study, approved by the Research Ethics Board of the IRCCS “Cà Granda Ospedale Maggiore Policlinico” (no. 2126; date: 17/10/2016), on otherwise healthy primiparous women. The inclusion criteria were age > 18 yr, absence of chronic respiratory or other severe pathology, and body mass index < 25 kg/m².

A cohort of nulliparous women served as control subjects. All of the recruited women gave written informed consent according to the Declaration of Helsinki.

Spirometry and lung volume subdivisions (total lung capacity, total gas volume, and residual volume) were measured with body plethysmography (BPd-HD; nSpire Health, Longmont, CO), whereas chest wall geometry, breathing pattern, and thoracoabdominal volumes were analyzed with optoelectronic plethysmography (OEP; Smart System BTS, Milan, Italy) (13).

In OEP, infrared light is emitted and received by a set of cameras, and dedicated software is used to reconstruct the three-dimensional (3D) coordinates of passive reflective markers (94 in seated position; 57 in supine position) placed on the trunk of the women according to specific anatomical points. Various geometric parameters were computed starting from the 3D mesh of points to characterize the dimensions of the chest wall. These included subcostal angle, heights, diameters, perimeters, cross-sectional areas, and volumes (Fig. 1). The volumes were also assessed in dynamic conditions during quiet breathing (QB) and a slow vital capacity (SVC) maneuver. The ventilatory pattern (duty cycle, respiratory frequency, tidal volume, and minute ventilation) was analyzed during QB.

An index of the velocity of shortening of the diaphragm was calculated as the ratio of abdominal volume variation at rest to inspiratory time and to cross-sectional area at the xiphoidal level (50, 58, 65).

An index of velocity of shortening of rib cage muscles was calculated as the ratio of rib cage volume variation at rest to inspiratory time and to the cross-sectional area obtained as the mean between the cross-sectional area at xiphoidal and Louis angle levels (5).

The SVC was split into its components: inspiratory capacity (IC) and expiratory reserve volume (ERV). The thoracoabdominal volume contributions at QB, SVC, IC, and ERV were also computed.

Finally, we used ultrasound (US) measurements to dynamically evaluate the diaphragm (Hawk 2102 EXL; BK Medical). We used a 12-MHz linear probe (B mode) to measure the thickness of the diaphragm as the distance between two echogenic layers, the pleural and peritoneal membranes. Measurements were performed at end-inspiration and end-expiration, and the difference between the two was divided by the value at end-expiration. The resulting ratio was defined as the diaphragmatic thickening fraction. The displacement of the dome of the diaphragm was defined as the maximal excursion (i.e., the difference between end-inspiration and end-expiration) on the vertical axis of the tracing (M mode, 5-MHz convex probe).

The measurements were performed at the end of the first (T₁), second (T₂), and third (T₃) trimesters of pregnancy in all pregnant women.

OEP and US were performed in all experimental sessions by single operators: an expert bioengineer and an experienced echographer, respectively. They were performed in both seated and supine positions to enable analysis of postural effect.

Statistical analysis. To evaluate the effect of the progression of pregnancy on all the acquired parameters, a one-way analysis of variance (ANOVA) or a Friedman ANOVA on ranks for repeated measures was performed if the parameter was normally or nonnormally distributed, respectively, with trimester of pregnancy as independent variable. At each trimester, to evaluate the difference between nulliparous and primiparous women, a one-way ANOVA or a Kruskal–Wallis ANOVA on ranks was performed if the parameter was normally or nonnormally distributed, respectively, with pregnant status as independent variable. The global effect of posture was tested with a *t* test or a Mann–Whitney rank sum test if the parameter was normally or nonnormally distributed, respectively, with posture as independent variable (SigmaStat version 11.0; Systat Software, San Jose, CA). For all parameters, the median and 25th and 75th percentiles of the changes between T₃ and T₁ were calculated (Excel, Microsoft Office Professional Plus 2016, Santa Rosa, CA).

Differences were regarded as significant for *P* values < 0.05. Data are reported as median and 25th and 75th percentiles in the text, table, and figures.

Some of these data were collected for the first time, and this was the reason for reporting absolute values, in order to provide reference values.

When planning the study, we could find no relevant published data on which to base a sample size calculation since available data were either measured with different and/or invasive techniques or reported with conflicting results. Although there are many studies evaluating

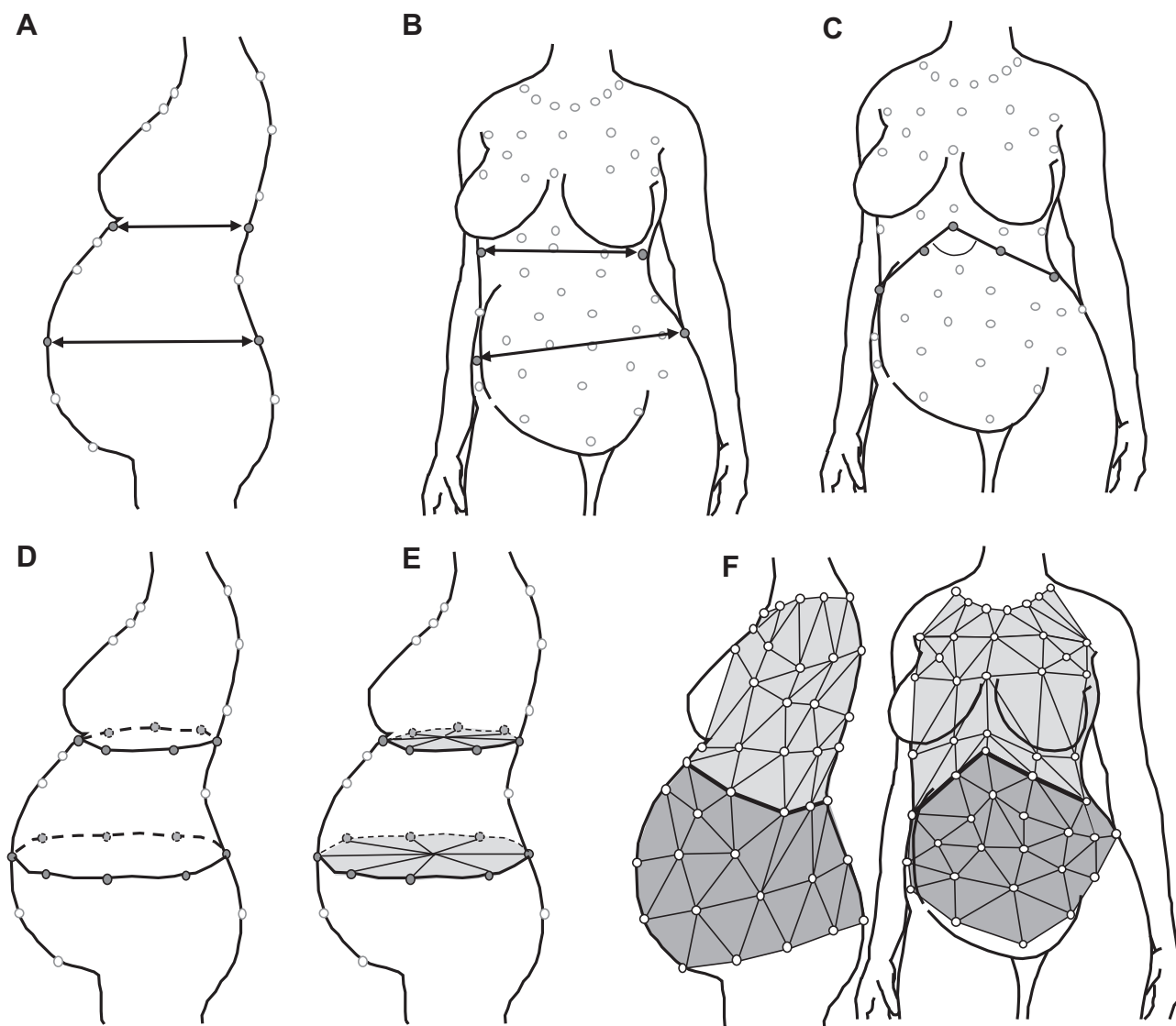


Fig. 1. Geometric parameters computed starting from the 3-dimensional (3D) mesh of points: antero-posterior diameters (A; as the distance between the anterior and posterior central markers placed at the same vertical level), medio-lateral diameters (B; as the distance between the 2 extreme markers at the same vertical level on the frontal plane), perimeters (D; obtained by summing the 3D distances of all the contiguous markers placed at the same vertical level), and cross-sectional areas (E; calculated by summing the areas of the triangles, each formed by 2 contiguous markers and the center of gravity of all the markers positioned at the same vertical level). They were measured at 2 different vertical thoracoabdominal levels: xiphoid process and umbilicus. In addition, the subcostal angle (C; computed considering the 3 central markers in correspondence of xiphoid and the 2 lateral markers defining the subcostal line), the height of the rib cage (as the distance between the clavicle and the lower costal margin), the height of the abdomen (as the distance between the lower costal margin and the iliac crest), and the volumes enclosed by the mesh of points of the chest wall and its 2 compartments, namely, the rib cage and the abdomen (F; through a triangulation of the 3D coordinates of the markers and the Gauss theorem) were also calculated.

both the primary outcome of the present study (diaphragm thickness assessed by US) and the secondary outcome (abdominal volume variations assessed by OEP), these methodologies have not been used before in pregnancy. In addition, when designing the study, the expected difference in the diaphragm induced by pregnancy was difficult to determine because we did not know which of the two opposite effects (stretching or conditioning) would prevail. The effect size was therefore uncertain because of the lack of previous studies. Because the main interest was the longitudinal change during pregnancy in each subject, a pilot study would have delayed the start of the study by at least 6 mo. There were therefore no data on which to base a proper power analysis. In addition, postexperiment power calculation is shown to be fundamentally flawed (31). The use of repeated-measures tests, however, enables detection of significant differences in the mean or median effect of treatment(s) within individuals

beyond what can be attributed to random variation of the repeated treatments.

RESULTS

The protocol was applied to 39 subjects: 18 primiparous and 21 nulliparous women with a mean age difference of 6 yr. Anthropometric data and gestational age are reported in Table 1. The primiparous women gained on average 6.5 kg until the 31st week of pregnancy.

Lung and chest wall volumes during maximal maneuver. The absolute value of vital capacity did not change with the progression of pregnancy. This was when the maneuver was both forced, as measured by spirometry, and slow, as measured

Table 1. Anthropometric data and gestational age at each trimester of pregnancy

	Nulliparous Women			Primiparous Women								
				1st Trimester			2nd Trimester			3rd Trimester		
	Median	p25	p75	Median	p25	p75	Median	p25	p75	Median	p25	p75
Age, yr	26.0	25.0	26.3	32.0§	31.0	33.5						
Height, m	1.69	1.63	1.72	1.63	1.60	1.65						
Weight, kg	57.0	54.8	63.3	57.2	53.8	62.3	59.2***	57.6	65.0	62.3***†††	60.1	69.4
BMI, kg/m ²	20.1	19.2	22.4	21.4	20.2	22.9	22.4***	21.3	23.3	23.4***†††	22.8	25.9
Gestational age, wk				15.0	13.8	17.0	21.0	21.0	22.0	31.5	31.0	32.0

Data are reported as medians and 25th and 75th percentiles (p25 and p75, respectively). BMI, body mass index computed as weight/height². *** $P < 0.001$ vs. 1st trimester; ††† $P < 0.001$ vs. 2nd trimester; § $P < 0.05$ vs. nulliparous women.

by OEP, and in both postures. Forced vital capacity remained within predicted values in all three trimesters (Fig. 2). Similarly, IC and ERV of the lung were both stable and not restricted with increasing maturation. Neither IC nor ERV of the chest wall changed across the three trimesters, with the exception of ERV in the supine position at T₃, which was lower than in control subjects (Supplemental Figs. S1 and S2; all supplemental material is available at <https://doi.org/10.6084/m9.figshare.8168045>). Absolute lung volumes remained unaffected by the progression of pregnancy (Supplemental Fig. S3). Abdominal ERV did not change in the three trimesters in the seated position ($P = 0.584$).

Chest wall geometry. With increasing gestation, chest wall geometry showed modifications at both thoracic and abdominal levels. As expected, all the abdominal geometric parameters progressively increased. In particular, chest wall volume increased by 4.46 L at T₃ (Supplemental Fig. S4). In contrast, the rib cage changed in shape (diameters, perimeters, cross-sectional areas, and costal angle progressively increased, but height decreased), whereas the volume remained constant (Fig.

3). Because total chest wall volume increased by 4.46 L at T₃, assuming an average density equal to 1, the 6.5 kg of weight gained was therefore mainly located in the trunk (~69%), mostly in the abdomen (~65%), with 31% in the extremities.

Breathing pattern during quiet breathing. Minute ventilation of primiparous women was higher than in the nulliparous group in the supine position in all trimesters but only slightly higher at T₃ in the seated position. Respiratory rate increased slightly in the seated position at T₂ and T₃, but not in the supine position, compared with T₁, whereas tidal volume remained unchanged in both postures (Fig. 4). Within the duration of a single breath, duty cycle represented the percentage of inspiratory time. Duty cycle did not differ with the progression of pregnancy in either the seated (T₁: 39.7%, T₂: 39.8%, T₃: 40.5%; $P = 0.584$) or supine (T₁: 40.9%, T₂: 40.7%, T₃: 41.2%; $P = 0.926$) position, being similar to nulliparous women (seated: 40.3%, supine: 41%; $P = 0.922$ and 0.683, respectively).

Thoracoabdominal contribution. At rest and during the maximal maneuver, breathing tended to be shifted toward the

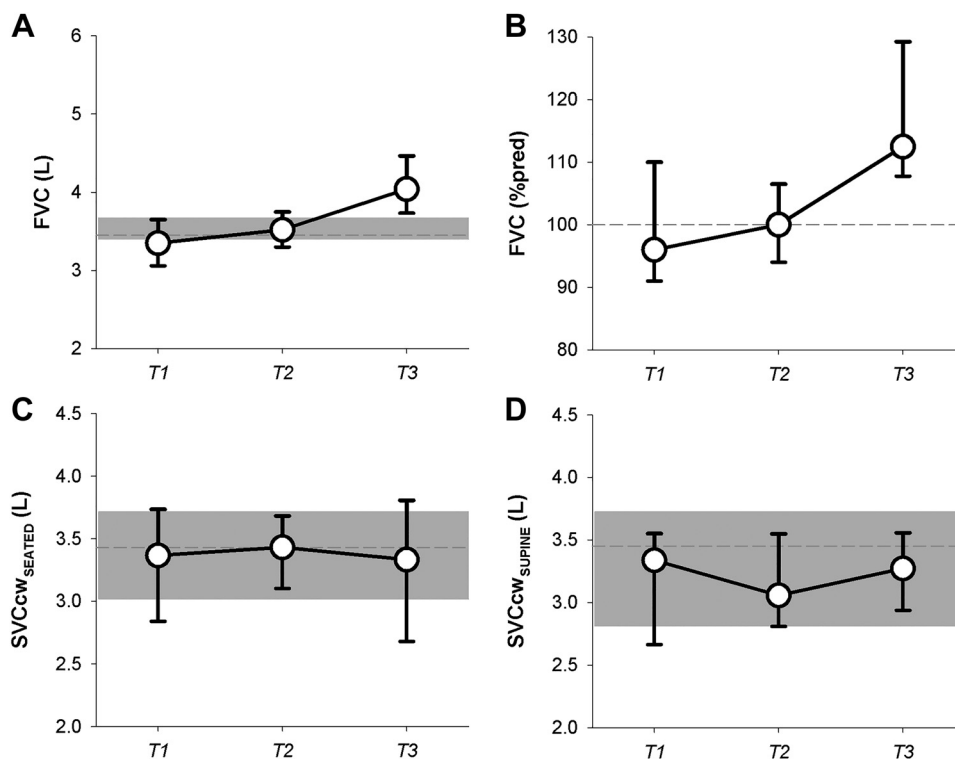


Fig. 2. Median (symbols) and interquartile range (whiskers) of spirometric forced vital capacity (FVC) expressed as absolute values (A) and % predicted (B) and slow vital capacity (SVC) measured with optoelectronic plethysmography in seated (C) and supine (D) positions during the 1st (T₁), 2nd (T₂), and 3rd (T₃) trimesters of pregnancy. The dashed gray line and the gray area represent the median and interquartile range, respectively, of the predicted values (A and B) or of the nulliparous women (C and D). CW, chest wall.

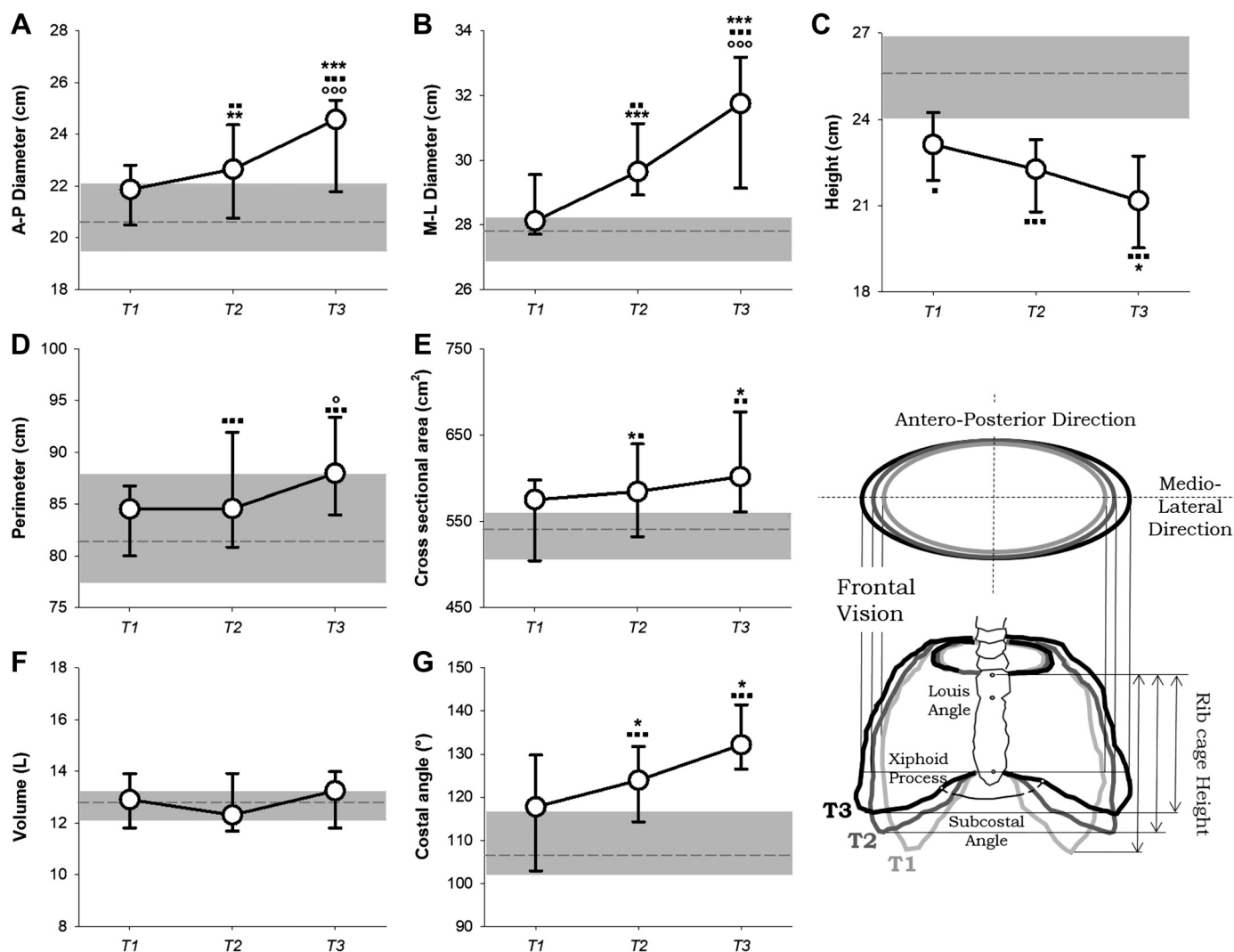


Fig. 3. Median (symbols) and interquartile range (whiskers) of antero-posterior (A-P) diameter (A), medio-lateral (M-L) diameter (B), perimeter (D), and cross-sectional area (E) measured at xiphoidal level as well as the height of the rib cage (C), its volume (F), and the subcostal angle (G) and an explicative schematic diagram (bottom right) summarizing the rib cage geometric changes during the 1st (T₁), 2nd (T₂), and 3rd (T₃) trimesters of pregnancy. The dashed gray line and the gray area represent the median and interquartile range, respectively, of nulliparous women. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. T₁; ○○ $P < 0.05$, ○○○ $P < 0.001$ vs. T₂; ■ $P < 0.05$, ■■ $P < 0.01$, ■■■ $P < 0.001$ vs. nulliparous women.

abdomen with increasing gestation. The abdominal contribution in pregnant women was generally greater at T₃ compared with the other two trimesters and compared with the nulliparous women in both postures. Of note, the abdominal contribution of ERV became negative at T₃ in the supine position (Fig. 5). The rib cage contribution, being complementary to the abdominal contribution, changed consequently (Supplemental Fig. S5).

Velocity of shortening. During QB, the estimated velocity of shortening of the diaphragm increased in the seated position at T₃ ($0.28 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$, $P < 0.05$; T₁: $0.22 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$ and T₂: $0.22 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$), whereas it did not change in the supine position (T₁: $0.35 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$, T₂: $0.37 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$, and T₃: $0.36 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$; $P = 0.148$). The estimated velocity of shortening of rib cage muscles at T₃ (seated: $0.42 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$; supine: $0.21 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$) became lower than at T₁ (seated: $0.53 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$, $P < 0.05$; supine: $0.25 \text{ mL}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}$, $P = 0.06$).

Ultrasound measurements. The thickness of the diaphragm, the thickness fraction, and the excursion of the diaphragmatic dome remained constant and within the range of nulliparous women along the three trimesters of pregnancy (Fig. 6).

Postural effect. Changing body position had similar effects on primiparous and nulliparous women. Passing from seated to supine position, minute ventilation decreased ($P = 0.016$ and $P < 0.001$, respectively); chest wall IC (IC_{CW}) increased ($P < 0.001$ and $P = 0.011$), whereas ERV_{CW} decreased ($P < 0.001$ in both groups). A significant increment occurred in the abdominal contribution to tidal volume ($P < 0.001$ in both groups), to SVC_{CW} ($P = 0.019$ and $P = 0.006$, respectively, in primiparous and nulliparous), and to IC_{CW} ($P < 0.001$ and $P = 0.011$, respectively), whereas the abdominal contribution to ERV_{CW} was reduced ($P < 0.001$ in both groups). In all women, the thickness of the diaphragm was 33% less in the supine compared with the upright position ($P < 0.001$ and $P = 0.007$), whereas the thickness fraction decreased only in the

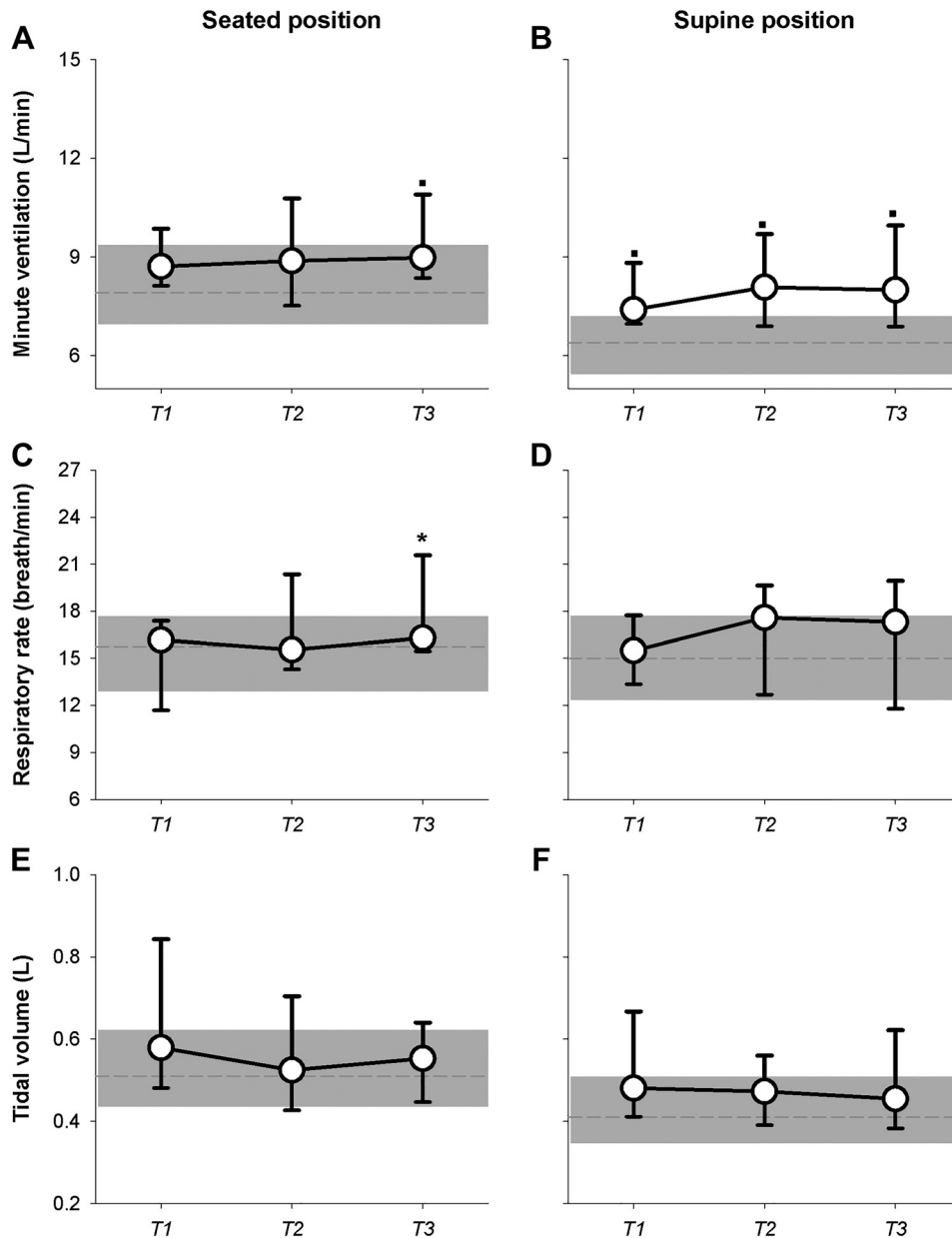


Fig. 4. Median (symbols) and interquartile range (whiskers) of minute ventilation, respiratory rate and tidal volume in seated (A, C, E, respectively) and supine (B, D, F, respectively) position during the 1st (T₁), 2nd (T₂), and 3rd (T₃) trimesters of pregnancy. The dashed gray line and the gray area represent the median and interquartile range, respectively, of nulliparous women. * $P < 0.05$ vs. T₁; ■ $P < 0.001$ vs. nulliparous women.

nulliparous group ($P = 0.033$). All the other parameters measured both supine and upright were unaffected by the changing of posture.

The differences of all the considered parameters between T₁ and T₃ were also computed (Supplemental Table S1).

DISCUSSION

In the present study, an original and comprehensive description of the respiratory changes with the evolution of pregnancy, using noninvasive measurements, is provided. Our main findings suggested that a reorganization of the rib cage geometry, in shape but not in volume, occurred during pregnancy. This process may be driven by the slow mechanical force developed by the growing uterus and mediated by pregnancy-induced hormonal changes. The new thoracic shape compensated for the growing uterus so that the lung was not restricted and space

for the abdominal expansion was accommodated. The abdominal contribution to inspiration increased, at rest and during maximal capacity. Despite the stretching effect of the cranial shift of viscera, diaphragm thickness was not diminished.

Pregnancy affects the respiratory system through two pathways, chemical and mechanical. The hormones (27, 52), per se, stimulate respiratory rate to increase (24). They also induce collagen loss with consequent joint relaxation (29). This, combined with the mechanical effect of the growing uterus, produces an upward bucket handle shift centered in the xiphoidal process and a reduction of rib cage height. In accordance with this, we found the rib cage to change in shape but not in volume. In this way, the lung was not restricted and space for the abdominal expansion was accommodated. The progressive geometric changes of the thoracoabdominal wall during gestation had different effects on the respiratory muscles. Breathing

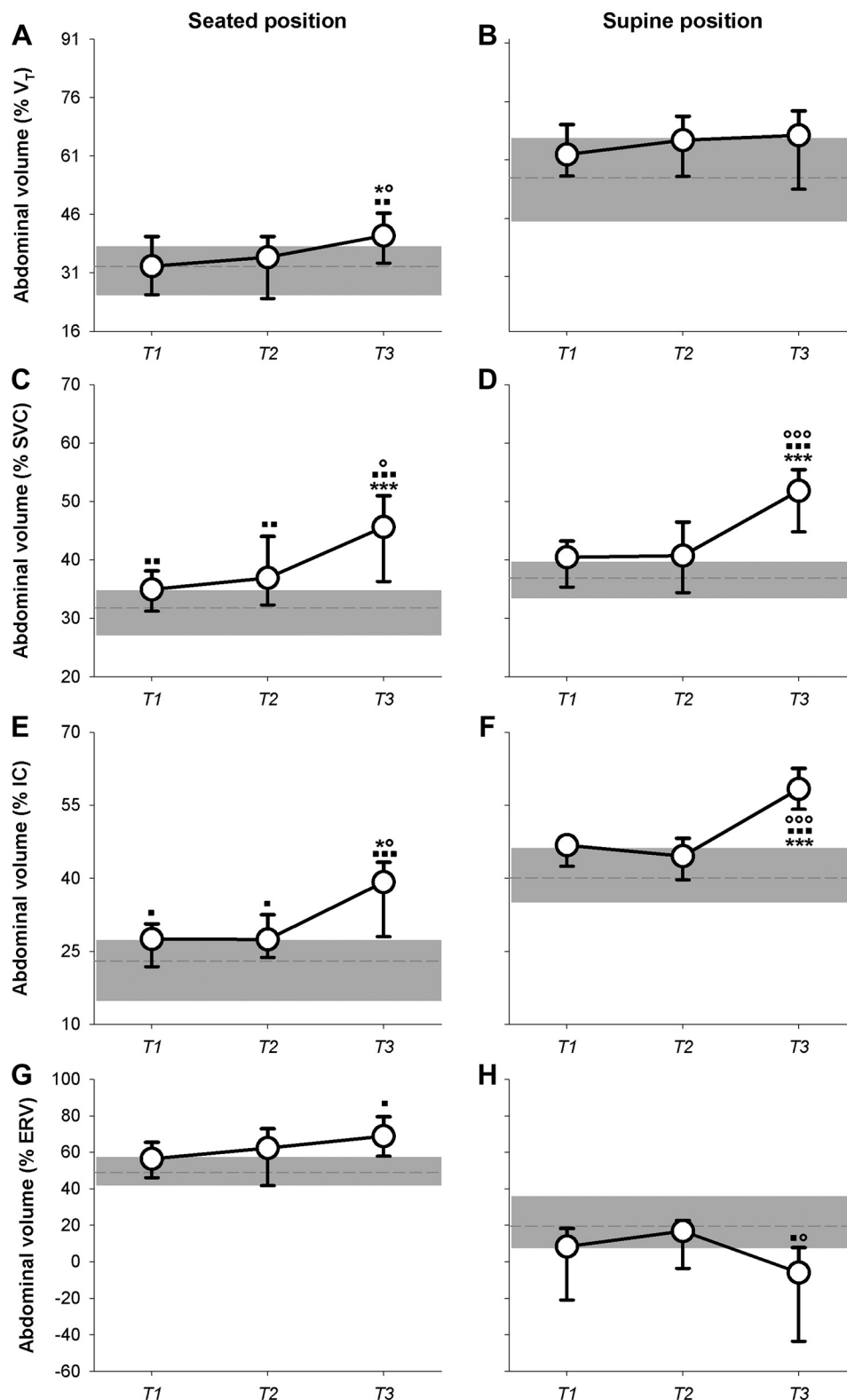


Fig. 5. Median (symbols) and interquartile range (whiskers) of the abdominal percentage contribution to the tidal volume (V_T), slow vital capacity (SVC), inspiratory capacity (IC), and expiratory reserve volume (ERV) in seated (A, C, E, G, respectively) and supine (B, D, F, H, respectively) positions during the 1st (T₁), 2nd (T₂), and 3rd (T₃) trimesters of pregnancy. The dashed gray line and the gray area represent the median and interquartile range, respectively, of nulliparous women. * $P < 0.05$, *** $P < 0.001$ vs. T₁; ○ $P < 0.05$, ○○ $P < 0.001$ vs. T₂; ■ $P < 0.05$, ■■ $P < 0.01$, ■■■ $P < 0.001$ vs. nulliparous women.

remained invariantly abdominal in the supine position, whereas the contribution of the abdomen increased in the seated position in the last trimester of pregnancy. This observation was in contrast with the findings of previous studies where breathing became more thoracic (14, 18). This conflicting result might be

explained by the different methods used to measure thoracoabdominal volume: the previous studies used two magnetometers, therefore deducing the volume variations by the displacement of only one thoracic and one abdominal diameter. In contrast, OEP allowed precise measurements of thoracoab-

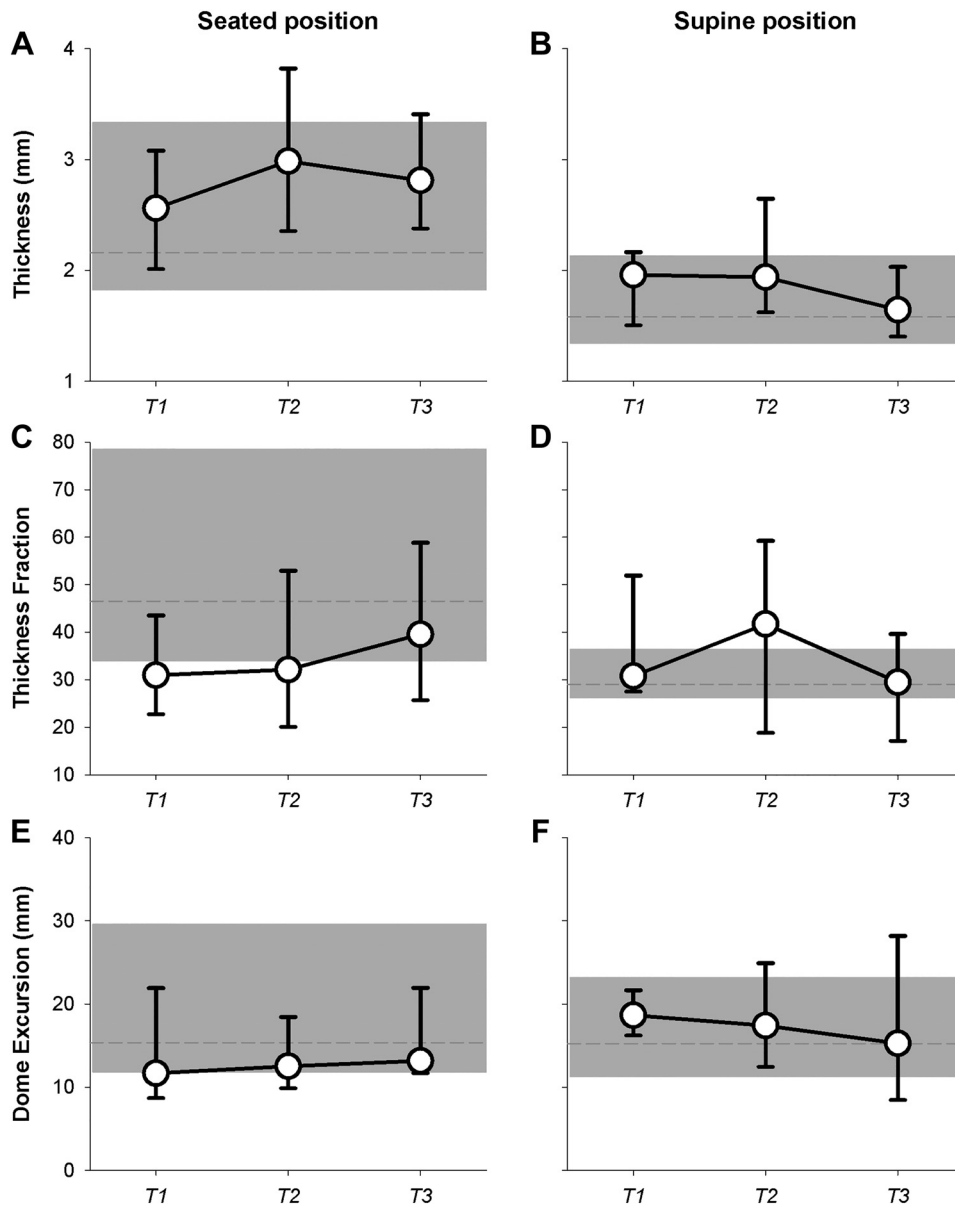


Fig. 6. Median (symbols) and interquartile range (whiskers) of the thickness, thickness fraction, and dome excursion of the diaphragm in seated (A, C, E, respectively) and supine (B, D, F, respectively) positions during the 1st (T₁), 2nd (T₂), and 3rd (T₃) trimesters of pregnancy. The dashed gray line and the gray area represent the median and interquartile range, respectively, of nulliparous women.

dominal volumes by considering a dense mesh of points from the clavicles to the iliac crest, according to anatomical points.

A didactic simplification of the actions of the diaphragm and rib cage muscles on the chest wall is that during inspiration abdominal and rib cage expansion reflect diaphragm and inspiratory rib cage muscle action, respectively, while expiration is passive at rest and driven purely by the elastic recoil of the respiratory system (4, 64). Conversely, expiration is active during vital capacity maneuvers, with expiratory rib cage and abdominal muscle contraction, the former contributing to reduce rib cage and the latter abdominal volume. The results of the present study, namely, the reduced contribution at T₃ of the rib cage to volume variations, during both spontaneous breathing and maximal maneuver, suggest that the action of the rib cage muscles was reduced during pregnancy. This was presumably due to the altered orientation of the ribs that shortened rib cage muscle length, thereby reducing the contractile force. It has been reported that a 10% variation of the angle between

ribs and vertebrae may lead to a 5% change in the force and work developed by intercostal muscles (51). In addition, at high lung volumes the orientation of the ribs also has a negative impact on the pleural pressure fall produced by a given cranial force applied to the ribs. This alteration in the pattern of rib motion is independent of muscle length and further inhibits rib cage muscle function (62, 63).

In contrast, abdominal muscles lengthen with pregnancy (68). We found that they increased their contribution during maximal expiration in the upright position, as indicated by the increased abdominal contribution at T₃ during the expiratory vital capacity maneuver. This happened despite diaphragm stretching that presumably developed greater passive tension, resulting therefore in a reduced transmission of intra-abdominal pressure (P_{AB}) to the pleural cavity during abdominal muscle contraction.

ERV did not change throughout pregnancy in either the supine or the upright posture, consistent with a constant lung

volume at end-expiration and with passive expiration during tidal breathing.

The growing uterus drives the pregnancy-induced changes in the diaphragm by affecting fiber length and abdominal pressure (2, 23).

It is known that the human pregnant uterus is contained in the pelvic cavity during the first trimester of pregnancy and expands into the abdomen during the second and third trimesters. As a consequence, there is a reduction of the abdominal cavity, a marked increase of the pelvic cavity, and a cranial shift of part of the abdominal organs determining diaphragmatic lengthening (1). If a material is stretched, it decreases its dimension transverse to the direction of stretching, therefore becoming thinner according to Poisson's ratio (53). The increasing abdominal pressure is applied uniformly to the abdominal surface of the diaphragm. This expands the operating length of the diaphragm during change of posture. Indeed, we showed that diaphragm thickness at end-expiration was reduced to one-third compared with the upright position in both groups of women. Despite the high interindividual variability, the ultrasound technique was able to detect this important thinning effect of posture even in nulliparous women, whose abdominal volume was significantly lower than that of pregnant women. In contrast, we hypothesize that the unchanged diaphragm thickness at end-expiration that we measured over pregnancy (i.e., under conditions of progressive diaphragm lengthening by the growing uterus) might actually be associated with an increased end-expiratory thickness (if measured at the same length), rather than with the variability introduced by measurement error, to progressively preserve resting muscle thickness.

The pregnancy-induced increase of ΔP_{AB} would infer an increased diaphragm inspiratory load and therefore, because the diaphragm is stretched, eccentric contraction during inspiration (49). Over time eccentric contraction of the diaphragm during tidal breathing would tend to increase diaphragm strength (22, 45), representing a form of muscle conditioning, which would be beneficial during parturition. However, in the absence of measurements of transdiaphragmatic pressure during a maximal inspiratory effort across trimesters, such observations remain mainly speculative. For ethical reasons, we did not use invasive methods in the present study.

Further studies should be designed to deeply explore the diaphragm during pregnancy in terms of length, thickness, electrical activity, action, force, and their relationships to determine the preserved diaphragmatic thickness. On the basis of the results of the present study, we propose a length-adaptive mechanism and/or a conditioning effect resulting in the development of higher force or simply counterbalancing the decreased abdominal compliance (14).

An additional limitation of this study was the lack of follow-up after delivery. Future studies should address the duration of any observed changes and adaptations that we have found. The study has, however, several strengths, namely, 1) the multidimensional parameters that have been measured to investigate different aspects of the pregnancy-induced changes in respiratory function; 2) the repeated measurements at each trimester of pregnancy in the entire cohort by single operators and in the same experimental session, therefore allowing concentration on the effect of the treatments rather than the differences between individuals; 3) the use of accurate and

noninvasive techniques without the use of any ionizing radiation (not compatible with the condition); 4) the detailed analysis of eupnea that can be a landmark for high-risk pregnancy when the condition of the mother does not allow maximal maneuvers; and 5) the results depending only on the pure effects of pregnancy without other cofactors like obesity, because of the small weight gain in the cohort of pregnant women.

The localized increased abdominal mass in the primiparous women might be compared to ascites. The mechanical effects of ascites on respiratory muscles are well elucidated, thanks to a series of animal studies (36–39). However, in such canine models the acute effects of ascites developed over a couple of hours are studied, rather than over months as during pregnancy. Acute ascites starts to have important respiratory effects after 200 mL/kg, in terms of reduced ability of both the diaphragm (36) and the abdominal muscles (38) to generate pressure, partially compensated by an increased force exerted by the parasternal intercostal muscles on the ribs (37, 39). These effects are opposite to the changes that we found during the progression of pregnancy. In addition, the threshold of 200 mL/kg would amount to 10 L of liquid for a woman of 50 kg like the primiparous women. At birth, the amniotic fluid is ~1 L (12) and the placenta is ~0.5 L (48) with an average baby of ~3.5 L. At the end of pregnancy, therefore, the amount of load/liquid in the abdomen is roughly 5 L. This estimation was supported by the 4.2 L of absolute abdominal volume increment that we found at T_3 , being far below the threshold quantity to induce respiratory problems in ascites. In addition, large-volume (range: 3.5–13 L) paracentesis changed neither the strength of inspiratory muscles nor thoracoabdominal kinematics in eight cirrhotic patients, although decreasing their overload and activation (19). It appears, therefore, that the effects of pregnancy on the respiratory muscles are different from those of ascites.

The study has potential clinical implications. The cocontraction of the diaphragm and abdominal muscles, a sort of “inspiratory-expulsive maneuver,” plays a fundamental role in the phase of baby expulsion, when the woman is asked to take deep inspirations followed by pushes, with intrauterine pressure increasing up to ~19 kPa (8). If the glottis is closed, this maneuver is called “closed-glottis” or “Valsalva” pushing. Alternatively, “open-glottis” pushing (9, 10, 54) implies no breath holding and slow exhalation so that P_{AB} increases to a lesser extent to avoid harmful consequences. The latter may be an ineffective strategy, despite the effort of the mother, because part of P_{AB} may be transmitted to the thorax through the relaxed diaphragm with possible wasting of the expulsive driving pressure and intrathoracic pressure rise to hamper venous return.

We have previously shown that expulsive maneuvers can also be performed by simultaneous contraction of diaphragm and abdominal muscles with open glottis, so that pleural pressure does not rise and almost all P_{AB} contributes to the expulsive force, therefore more efficiently, with blood shifting in the order of 5 mL/cm²H₂O increase in P_{AB} (3, 7).

We can speculate that the length-adaptive mechanism and/or the conditioning effect is established to preserve the diaphragm from pregnancy-induced changes in a way to have an active role during parturition by contributing to the expulsive force, resisting the upward displacement and minimizing the rise in

pleural pressure. In addition, our results help to explain, at least in part, why upright positions are considered safer and suitable for more effective pushing (54, 57). The supine position seemed to hinder the action of abdominal muscles during forced expiration at T₃, because ERV was lower and entirely accomplished by rib cage muscles with paradoxical outward motion of the abdomen indicating less efficient action of the abdominal muscles.

Future studies should address which is the most efficient strategy and positioning of pushing that maximizes the expulsive effect of the respiratory muscles.

In conclusion, the physiological and structural adaptations of the chest wall that occur during pregnancy preserve lung volumes as well as diaphragm and abdominal muscle function at the expense of rib cage strength. Knowledge of these normal physiological changes during pregnancy may be helpful for the clinician dealing with high-risk pregnancies.

ACKNOWLEDGMENTS

The authors thank all the babies (and their mothers) who kindly participated in the study, Chiara Pizzamiglio and Luciana Fava for precious support, Emilia Privitera for the organization, and Renata Riha, who stimulated the conception of this work.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.L. and I.R. conceived and designed research; A.L., D.A., G.B., M.D., F.B., and I.R. performed experiments; A.L., G.B., and M.D. analyzed data; A.L. interpreted results of experiments; A.L., G.B., and M.D. prepared figures; A.L. drafted manuscript; A.L., A.A., and P.F. edited and revised manuscript; A.L., A.A., P.F., D.A., N.P., F.B., M.N., and I.R. approved final version of manuscript.

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