Pregnancy blood test dynamics resemble rejuvenation of some organs and aging of others

Ron Moran[1], Glen Pridham[1], Yoel Toledano[2], Uri Alon[1*]

[1]Dept. Molecular Cell Biology, Weizmann Institute of Science; Rehovot, 7610001, Israel
[2]Division of Maternal Fetal Medicine, Helen Schneider Women's Hospital, Rabin Medical Center; Petah Tikva, 4941492, Israel

*Corresponding author. Email address: urialonw@gmail.com

Abstract

Aging and pregnancy both involve changes in many physiological systems. Some of these changes are similar, leading to suggestions that pregnancy may be a model for aging. Recent studies using DNA methylation clocks showed apparent aging during gestation which resolves postpartum. Since aging and pregnancy are complex, it is important to compare them in terms of many physiological parameters and at many time points. Here, we analyzed cross-sectional data on 62 lab tests at weekly resolution in 300,000 pregnancies and 1.4 million nonpregnant females aged 20-80. We trained a regression model to predict age from lab tests. Apparent age dropped by 8 years in early pregnancy, rose by 30 years towards delivery, and recovered postpartum. Certain systems exhibited "rejuvenation," with opposite trends in pregnancy and aging, including renal, iron, and most liver tests. Others, such as coagulation, thyroid, muscle, and metabolic systems, showed apparent aging. Some systems displayed mixed trends. Notably, in the systems that showed apparent aging, the physiological mechanisms for the changes differed between pregnancy and aging. Pregnancy complications led to an additional apparent aging of 4-8 years. We conclude that pregnancy is a superficial model of aging that involves different mechanisms and rejuvenation or aging-like changes in different systems. Nevertheless, apparent age may be a convenient way to measure magnitude and direction of physiological perturbations.

Introduction

Both pregnancy (Bar et al. 2025; Mockridge and Maclennan 2019a) and aging (López-Otín et al. 2023; Moqri et al. 2023) are associated with stress on the body and involve changes in many physiological systems. Some of the changes in pregnancy resemble changes in aging, such as a shift in immunity towards innate immunity (Abu-Raya et al. 2020; Castelo-Branco and Soveral 2014) and reduced red blood cell counts (Bar et al. 2025; Paliogiannis et al. 2018). This has led to the suggestion that pregnancy may be a model for aging (Andrawus et al. 2023; Giller et al. 2020). For example, pregnancy and its complications involve inflammation, oxidative stress and

telomere changes (Han et al. 2021; Leal et al. 2011; Omu et al. 1999; Pollack, Rivers, and Ahrens 2018; Ryan et al. 2024), and similar changes also occur in aging.

The relation of pregnancy to aging has recently gained attention due to aging clocks. Aging clocks are statistical models designed to predict biological age from molecular cues, where biological age is defined as the age at which the mean population has an equivalent state of health to the individual (Moqri 2023). A major advance was the advent of clocks based on DNA methylation (Hannum et al. 2013; Horvath 2013) in 2013 - several hundred methylation sites out of millions could accurately predict chronological age. Biological age acceleration was based on the residuals between true and predicted chronological age.
Next-generation clocks were trained directly on risk of morbidity and mortality, improving their specificity to biological age. These clocks were recently extended to the level of individual organs (Levine et al. 2018; Moguilner et al. 2024; Mongelli et al. 2023; Shireby et al. 2020). Many clocks use additional molecular cues such as proteomics data (Argentieri et al. 2024) and blood tests (Bortz et al. 2023). Using first- and second-generation clocks, a higher biological age was registered during pregnancy (Pham et al. 2024; Poganik et al. 2023), which recovered after delivery.

If pregnancy and aging are related, knowledge may be transferred to treat aging related diseases; similarly, if pregnancy shows rejuvenation, it may inspire approaches for slowing aging. However, pregnancy and aging are complex and involve many systems. It is therefore worthwhile to make a detailed system-by-system comparison. Furthermore, the clock studies on pregnancy involve only one or two timepoints during gestation and one point postpartum. Higher temporal resolution can help resolve the dynamics of each trimester and the different stages of postpartum adaptation (Bar et al. 2025).

To compare aging and pregnancy, we study 62 laboratory (lab) blood tests comprising all major physiological systems from a nationwide dataset from the Clalit healthcare services (Balicer and Afek 2017; Cohen et al. 2021). We use cross-sectional data from 313,000 pregnancies in weekly bins (Bar et al. 2025) and compare this to cross-sectional data from 1.4 million nonpregnant females at ages 20-80 (Cohen et al. 2021). We develop a blood test aging clock and compare effective clock age per test and per system, each week from 60 weeks before delivery to 80 weeks after delivery, spanning preconception, gestation and postpartum periods.

During pregnancy, apparent lab-test age dropped by 8 years in the first trimester and then rose linearly, peaking at 30 apparent years older than baseline. After delivery, apparent age recovered gradually over a year postpartum. Several organ systems showed apparent rejuvenation - opposite changes in aging and gestation - including renal, iron and most liver tests. Other systems showed apparent aging - changes in the same direction in aging and gestation - such as coagulation, thyroid, muscle and metabolic tests. A few systems showed mixed directions compared to aging. Complications of pregnancy – pre-eclampsia and gestational diabetes - showed aging-like changes of 4-8 years compared to healthy pregnancies. The physiological mechanism underlying the test changes differed between pregnancy and aging.

Results

Lab-test 'age' drops during the first trimester, rises in the second and third, and resets over months postpartum

To evaluate the effective lab-test age during each week of pregnancy and postpartum, we developed a lab-test aging clock (see Methods), based on linear regression between binned lab test mean values and chronological age. Reference values for healthy females are from LabNorm by (Cohen et al. 2021). We call this regression model LabAge.

LabAge predicts chronological age with r=0.87, p-value <0.001, like other aging clocks that use blood tests (Bortz et al. 2023; Putin et al. 2016). The goal here is to provide a measure in years for the apparent aging and rejuvenation of tests during pregnancy and postpartum. The lab tests that contributed the most to LabAge are urea, systolic blood pressure, the glycemic test HbA1c, LDL cholesterol, creatinine, red blood cell distribution width RDW-sd and Albumin; all rise with age except albumin which decreases. The weights for each test are shown in Fig 1.

We applied LabAge to pregnancy cross-sectional data binned by weeks. For each week we used the mean test value of all participants tested in that week. The dataset (Bar et al. 2025) spans a period starting from 60 weeks before delivery to 80 weeks after delivery. Each lab test is evaluated in terms of quantiles of a reference population of healthy age-matched non-pregnant females from (Bar et al. 2025) (see Methods).

The LabAge clock provides an age for each week of pregnancy according to the lab test data. Apparent lab-test age drops in the first trimester by about eight years, then rises linearly with gestation week peaking at delivery with an apparent aging of 30 years above preconception (Fig 2). Clock age then recovers halfway at ten weeks postpartum, and another halfway at 60 weeks postpartum. The postpartum period thus shows fast (< 10 weeks) and slow (3 < months) recovery phases.

Fig 1. Weights for the lab test regression clock (LabAge). Tests are grouped according to system. Folic acid (FA) and hemoglobin related RBC tests are grouped with iron tests. sCr is serum creatinine. Full test names are in table S1. Weights are derived from a model trained on a z-scored dataset for comparability.

Fig 2. LabAge change in gestation and postpartum. Change in lab test clock age (LabAge) at each week of gestation and postpartum where age 0 is baseline clock age at 60 weeks before delivery. Gestation is in gray background with delivery at t=0. Errors (shaded) are 95% confidence interval (CI) from resampling (see Methods). Outliers were corrected using the empirical distribution per weekly bin (see Methods).

Some systems show apparent rejuvenation, while others show apparent aging

We calculated an effective age for each test using the regression model. In Fig 3, the test ages are grouped by physiological systems. We computed the effective age change for each system using these grouped tests (black curves in Fig 3). Most systems have one or two tests that contribute most strongly to its effective age.

Based on the lab tests, the renal and iron (including hemoglobin) systems show the greatest apparent rejuvenation. Conversely, other systems show apparent aging. The largest effects are in the metabolic, hepatic and musculoskeletal systems, followed by immune, RBC, coagulation and thyroid systems. In the first trimester, some changes are opposite to the second and third in several systems like coagulation, iron, muscle and metabolism. After delivery many systems recover within weeks. In the postpartum period, some systems, like the immune system, show an undershoot, whereas the renal system displays a sizable overshoot. The slowest postpartum recovery is in the musculoskeletal and metabolic systems. We provide more details on each system next.

Fig 3. Apparent age per week of pregnancy and postpartum by test and system. Thick black lines are the total change per system, and individual test age traces are labeled and in colors. Gestation is in gray background; delivery is at t=0. Total changes sum up to the effective age difference in Fig. 2.

Renal and iron lab-test changes in pregnancy are opposite to those in aging - apparent rejuvenation

To further compare the effects of aging and pregnancy, we plot in Fig 4 the maximal quantile change during gestation versus the quantile change between age 20 and 80 for all tests. Apparent aging occurs along the first and third quadrants, and apparent rejuvenation along second and fourth quadrants.

Renal tests including electrolytes, urea and creatinine showed sizable changes in both aging and gestation, but these changes had opposite directions as shown in Fig 4. This apparent rejuvenation during gestation reflects the increase in glomerular filtration rate (GFR) during pregnancy of 30% (Cheung and Lafayette 2013), and the 40% decrease in GFR over aging (Glassock and Winearls 2009).

Tests related to iron and hemoglobin also showed opposite directionality in pregnancy and aging. Hemoglobin and ferritin dropped in pregnancy and rose in aging, and transferrin rose in pregnancy and dropped in aging. This reflects aspects of mild anemia found in pregnancy (Bar et al. 2025; Fisher and Nemeth 2017; Shand and Kidson-Gerber 2023) and excess iron found in aging (Zeidan et al. 2021). Folic acid tests are affected by pregnancy supplements and rise in pregnancy (Amitai et al. 2008) but are unaffected in aging.

Liver test changes in pregnancy are mostly opposite to those in aging - indicating apparent rejuvenation - except for albumin

Two other systems showed coherent changes in pregnancy that were largely opposite to those of aging (Fig 4). Liver tests that represent hepatocellular dysfunction, e.g. ALT and AST dropped in pregnancy and rose in aging.
Two liver tests showed changes as in aging, dropping with age and gestation - albumin and total protein. Indeed, they are strongly correlated tests. However, the origin for this decline is different in aging and pregnancy. During pregnancy, the drop reflects increased hemodilution due to the 50% rise in blood volume (Mockridge and Maclennan 2019b), whereas in aging they represent decline in liver albumin production during aging (Cooper and Gardner 1989; Salive et al. 1992).

Coagulation, thyroid, muscle and metabolic tests show apparent aging during gestation

Coagulation tests indicate a hypercoagulative state in both aging and gestation (Fig 4). Hypercoagulation in gestation is thought to be protective (Thornton and Douglas 2010) since delivery is associated with blood loss. Aging is also associated with hypercoagulation. However, it may be detrimental in old age. It is suggested to be an aspect of inflammaging (Walston et al. 2002) and linked to endothelial dysfunction (Herrera et al. 2010).

For the metabolic system, lipid tests and BMI increase both in gestation and aging. The lipid profile includes serum LDL, triglycerides and total cholesterol (Fig 4). Pregnancy is associated with weight gain and increased BMI. It is mainly attributed to elevated blood and amniotic fluid volume and the growing fetus (Kominiarek and Peaceman 2017). Alternatively, in aging the rise in BMI is driven mostly by higher fat mass, which partially explains the elevated fatty metabolites (Johnson and Stolzing 2019; Landsberger, Amit, and Alon 2024; Ponti et al. 2020)

Glycemic indices show complex dynamics during gestation. The maximal trend is negative. Hence, it is opposite to the rise of aging. Again, the mechanisms are distinct (Newbern and Freemark 2011). Glycemic metabolic pathways are regulated in pregnancy by placental hormones and by the demands of the embryo. In aging, insulin resistance rises among other changes to cause an increase in glucose in many individuals.

The thyroid axis in pregnancy shows a suppression of serum thyroid stimulating hormone (TSH), partly due to the TSH-like effects of the placental hormone human chorionic gonadotropin (hCG) (YOSHIMURA and HERSHMAN 1995). A reduction of free Thyroxine (FT_4) is also noticeable. Both pregnancy and aging show a drop in free triiodothyronine (FT_3). During gestation, this is due to increased renal iodine clearance and higher expression of thyroid binding globulin (TBG) (Burrow, Fisher, and Larsen 1994). On the other hand, aging is associated with a reduced metabolic demand which affects the deiodination of T_4 to T_3 . Moreover, the euthyroid sick syndrome related to inflammation and chronic illness is more prevalent in old age (Chatzitomaris et al. 2017; Garasto et al. 2017; Hoermann et al. 2014).

The musculoskeletal system shows changes aligned with aging. One of the lab tests that changes most in pregnancy, serum alkaline phosphatase, rises also in aging, in part due to the expression of a placental variant of the alkaline phosphatase enzyme (McMaster et al. 1964).

Red blood cell dynamics and immune system tests present mixed similarity with aging

Immune and red blood cell tests display a more complex picture (Fig 4). More immune-related blood tests fluctuate in pregnancy than in aging. The test that varies most in aging is a reduction in lymphocytes. It shifts in a similar direction as in pregnancy (Chandra et al. 2012). The mechanisms in both states are distinct. In pregnancy, the adaptive immune system is redirected to avoid attacking the embryonic tissues (Abu-Raya et al. 2020; Jamieson, Theiler, and Rasmussen n.d.). In aging, thymic involution and other alterations drive a reduction in lymphocyte counts (Ferrucci and Fabbri 2018; Navarro-Martínez and Cauli 2021).

Generally, red blood cell tests shift during gestation and aging in the same direction. Specifically, cell count (RBC) drops while mean cellular volume (MCV) and red blood cells distribution width (coefficient of variation, RDW) both rise (Chandra et al. 2012; Hoffmann, Nabbe, and Broek 2015; Paliogiannis et al. 2018). However, the hematocrit shows opposite effects, rising in aging and dropping in pregnancy. Probably, the latter effect is due to hemodilution (Mockridge and Maclennan 2019a; Sanghavi and Rutherford 2014).

Fig 4. Changes in aging versus pregnancy show apparent rejuvenation or aging in different tests and systems. Maximal quantile change (max-min) in gestation versus change in aging between age 20 and 80 (see Methods) in quantile score of the reference population (healthy nonpregnant females). Quadrants 1 and 3 (pink) denote changes in the same direction

and are labeled 'aging', and quadrants 2 and 4 (green) denote changes in opposite directions and are denoted 'rejuvenation'. Error bars are 2 standard deviations (see Methods).

Pregnancy complications display lab test "aging" relative to a healthy pregnancy

We compared the LabAge of healthy pregnancies to three of the most common severe pregnancy complications: pre-eclampsia, gestational diabetes and postpartum hemorrhage (Fig 5). Pre-eclampsia involves high blood pressure, organ damage and risk of seizures, gestational diabetes is hyperglycemia without history of a previous diabetes, and postpartum hemorrhage involves severe bleeding which can be life threatening. Data is from Bar et al (Bar et al. 2025).

Pre-eclampsia and gestational diabetes cohorts showed LabAge that is about 5 years older than healthy pregnancy. This increased lab test age appears also before gestation, because the population of women at risk differs from the general population. Women with both complications exhibit metabolic derangements and inflammation markers which also characterize aging (Giller et al. 2020). For example, some alterations include elevated glucose, serum LDL cholesterol, blood pressure and BMI levels.

Postpartum hemorrhage did not show a significant aging effect. It occurs at delivery and may not involve physiological changes as pronounced as the other two complications, which are diagnosed during gestation (Anon 2017; Wagner 2004; Ye et al. 2022).

When comparing the changes test by test, a pregnancy complicated by pre-eclampsia and gestational diabetes differs from a healthy pregnancy in a direction that aligns with aging (Fig S1).

Fig 5. Pregnancy complicated by pre-eclampsia and gestational diabetes shows higher apparent age than healthy gestation. A. pre-eclampsia n=5643 pregnancies b. Gestational diabetes, n=7244 c. postpartum hemorrhage n=4574 . Data is grouped by 4-week intervals. Statistical significance (one way z test) for positive age was computed for preconception, for each trimester and for early and late postpartum with dashed lines demarcating these periods. Significance is denoted by *p<0.05, ** p<0.01 with multiple hypothesis testing correction (Benjamini Hochberg). Errors (shaded) are 95% CI from resampling (see Methods).

Discussion

We compared the weekly changes in 62 lab tests during pregnancy to their changes during aging, using cross-sectional data from 313,000 pregnancies and 1.4 million nonpregnant females at ages 20-80. The results highlight that while pregnancy and aging share interesting gross physiological changes, they are nevertheless unique processes involving quite different biological mechanisms. Apparent lab-test age during pregnancy dropped by 8 years in the first trimester and rose by 30 years towards delivery, recovering gradually over months postpartum. Several systems showed apparent rejuvenation including renal, iron and most liver tests. Other systems, e.g. such as coagulation, thyroid, muscle and metabolic tests, presented apparent aging. A few systems showed mixed directions in pregnancy vs. aging. Complications of pregnancy showed aging-like shifts of about 5 years compared to healthy pregnancies.

In the systems that showed apparent aging, the reasons for the changes differ between healthy pregnancy and aging. For example, blood volume grows by about 50% over gestation causing hemodilution (Mockridge and Maclennan 2019b), and thus tests for serum proteins like albumin drop during pregnancy. Albumin also drops during aging, but for different reasons, primarily a decline in its liver production rate and due to chronic inflammation as a negative acute phase response (Alberro et al. 2021; Ferrucci and Fabbri 2018; Gruys et al. 2005). Another major physiological difference is the involvement of placental hormones which are absent in aging. These hormones cause many changes in lipids, glucose, coagulation, musculoskeletal, immune tests and others.

The apparent rejuvenation of renal tests stems primarily from the rise in glomerular filtration rate (GFR) over gestation, by a factor of about 30%, starting in the first trimester. This rise is driven by systemic vasodilation, plasma volume expansion, and hormonal influences, including relaxin, progesterone, and estrogen. Collectively, they reduce vascular resistance and enhance renal perfusion (Cheung and Lafayette 2013; Lopes van Balen et al. 2019) . In aging, GFR gradually declines due to reduced cardiac output and accumulating kidney damage causing lab tests to shift in the opposite direction.

The apparent rejuvenation of iron related tests stems from increased iron storage during aging (Zeidan et al. 2021), and an increased demand for iron during gestation (Fisher and Nemeth 2017).

Pathological pregnancy complications such as pre-eclampsia and gestational diabetes show proinflammatory and other changes that are like effects seen in aging. Our analysis of these complications indicates that they differ from healthy pregnancy in a way that aligns with changes in aging. They add an apparent 5 years to the LabAge lab test clock. This apparent aging exists before pregnancy and does not change significantly with gestation and postpartum, suggesting that it is a characteristic of the population susceptible to these pregnancy complications. In contrast, postpartum hemorrhage which manifests after delivery did not significantly alter lab test age compared to healthy pregnancy. High LabAge may be an indicator of risk; it would be

of interest to construct classifiers to predict pregnancy complications, but the present cross-sectional nature of the data does not allow us to do so in the present study.

A broad conclusion of this study is that effective lab test age can be a convenient metric with units of years to compare tests and systems in physiological situations such as pregnancy. However, the physiological reasons for a given change are usually different between pregnancy and aging. A transient rise in methylation clock age is also seen in surgery, COVID-19 and other conditions (Poganik et al. 2023) and may thus measure not aging per se, but rather physiological stress . One potential advance would be to develop accurate clocks for biological age based on molecular mechanisms specific to aging rather than general lab tests or methylation. Thus, it may be possible to avoid being confounded by physiological and stochastic (Min et al. 2024; Rutledge, Oh, and Wyss-Coray 2022) responses that are not related to aging.

We conclude that an ageing clock can provide a convenient measure of physiological perturbations with units of years. This can help to compare processes that are very different such as aging and pregnancy. Using cross-sectional data with high temporal resolution the complexity of physiological change in pregnancy, with some systems showing apparent rejuvenation and others apparent aging. Interestingly, opposite effects were documented in the first trimester compared with the second and third trimesters. The postpartum recovery occurred rapidly within weeks and then more slowly within about a year.

Methods

Study population (pregnancy dataset)

The study population consists of Clalit healthcare members who were pregnant in the years 2003-2020 aged [20,35]. Only healthy pregnancies were considered except as noted. Due to privacy considerations, the analysis was on summary statistics on participants who took the lab tests in each weekly bin. Individualized data are not available. For more information see Bar et al (Bar et al. 2025).

Reference Population

Lab test distributions of healthy, non-pregnant female populations parameterized by age are from LabNorm (Cohen et al. 2021). For each age in the reference of [20,80], we drew 20 samples for each of the tests based on LabNorm quantiles.

Linear regression

The LabAge clock model was based on ordinary least squares regression using the python module statsmodels.api.OLS. CI on the parameters was computed using statsmodels.regression.linear_model.RegressionResults.conf_int with 95%. We trained the regression model on reference data from LabNorm. Each test has reference values for ages 20 to 89 for females. Pearson r was reported between predicted and sampled age. All tests used are shown in table S1.

Maximum quantile difference in pregnancy dataset

We constructed a distribution parameterized by the mean quantile score and standard deviation for each gestational week (measured by 0 as delivery) indexed by i and lab test indexed by t:

$$\alpha_{t,i} \sim \mathcal{N}\left(\mu_{q_{t,i}}, \frac{\sigma_{q_{t,i}}}{\sqrt{n_{t,i}}}\right), \forall (t,i), n \gg 1$$

We sampled over the gestation weeks $\alpha_{t,i}, \forall i \in [-38,0]$. We calculated the maximal difference for each such sampling indexed by j:

$$diff_{t,j} = \max_i \alpha_{t,i,j} - \min_i \alpha_{t,i,j}$$

To resample, we repeated for 1000 j's and reported the mean and CI of 2 standard deviations ~97%.

Quantile difference in aging

To compute the quantile difference between age 80 and 20, we estimated the age 80 value by the median LabNorm values at the age range $\in [75,84]$ for healthy females. If there was a significant change within this age range, as defined by regression p value <0.05, we used the residuals of the regression at age 80. We then transform these values into quantiles relative to the reference population at age 20 and subtract 0.5 which is the mean quantile score by definition. CI is 2 standard deviations ~97%.

CI for LabAge

Mean values per gestational week and test were resampled 1000 times as above. Parameters from the regression were sampled assuming normality 1000 times for each weekly bin i. We report the resampling mean and the CI of 1.96 standard deviations ~95%. In Fig 5, The weekly bin of delivery was excluded due to high variance across all lab tests.

Outlier correction

Some weekly bins in some tests have strong outliers shifting the mean and standard deviation. For test t and weekly bin i, we deemed that the standard deviation cannot exceed 10 times the difference between the 95th and the 5th percentiles:

$$is\_outlier = \sigma_{t,i} > 10 \cdot \left(v_{(0.95)} - v_{(0.05)}\right)$$

We corrected such outliers using a linear approximation of the distribution of the weekly bin. Denoting the PDF as $\widehat{f_{t,\iota}}$:

$$\widehat{f_{t,\iota}}(x) = \sum_j b1_{[q_j, q_{j+1}]}(x) \cdot \frac{q_{j+1} - q_j}{v_{t,i,(q_{j+1})} - v_{t,i,(q_j)}}$$

Extrapolating left to $q_0 = 0$ and right to $q_{\max i+1} = 1$ and vanishing outside. We calculated the mean and standard deviation by definition for continuous CDF $\widehat{F_{t,\iota}} = \int \widehat{f_{t,\iota}}$.
The uncorrected prediction in Fig 2 is given in fig S2.

p-values in the pregnancy complications prediction (one-way z-test)

LabAge of the reference was subtracted from LabAge of each complication. For each gestational period (preconception, trimesters, early and late postpartum) we pooled all LabAges and calculated $z_{statistic} = \frac{\mu}{\sigma}$. We reported the p-value as: $1 - \Phi(z_{statistic})$. FDR used Benjamini Hochberg for the 6 p-values.

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Author contributions

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Software: RM
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Competing interests

The authors declare that they have no competing interests.

Data and materials availability:

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. The source code and data used to perform the analysis is available at the GitHub repository as of the date of publication. The repository is open for public use:

https://github.com/AlonLabWIS/PregAging

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