

# Ultrasonographic Evaluation of Embryonic Cardiac Development

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## ABSTRACT

The heart is the first functional organ in the human embryo and starts to beat by 4 weeks of development. Recently, progressive advances in medical ultrasonography, especially high-frequency transvaginal ultrasonography and the color Doppler equipment allow access to the developing embryonic human heart. The anatomical and functional characteristics of the embryonic heart are different from those of the fetus and neonate. Embryo crown-rump-length (CRL) at 2 mm shows a discernible heartbeat. At this time, the embryonic heart is in the cardiac tube stage. Embryo CRL at 5 mm shows distinct differential movements of the ventricles and atria (13th Carnegie stage, 6+4/7 gestational weeks). At the 7th gestational weeks, an interventricular septum can be visualized in the embryonic heart. Although a heartbeat can be detected and gross cardiac structures are visualized early in gestation, visualization of some embryologically important intracardiac structures, such as the endocardial cushion, atrioventricular foramen, or atrioventricular valves are still limited, even with the latest high-end equipment. Cine function and color Doppler provide some valuable information about the morphology and function of the developing embryonic heart. For the evaluation of the embryonic heart using ultrasonography, keep the principle of "As Low As Reasonably Achievable" (ALARA) and the least use of color Doppler and pulsed Doppler.

**Keywords:** Embryo, Heart, Ultrasound.

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## INTRODUCTION

The heart is the first functional organ in the human embryo and starts to beat by 4 weeks of development.<sup>1</sup>

At around 18–19 days after fertilization (4 weeks 4 days–4 weeks 5 days of gestational age, GA), the heart begins to form. This process begins with the formation of two cardiac tubes that merge to form the single tubular heart. The single cardiac tube shows five distinctive serial regions: from tail to head, these are the sinus venosus, primitive atrium, primitive ventricle, bulbus cordis, and truncus arteriosus (Fig. 1). Simultaneously, the cardiac tube begins looping within the pericardial cavity. The sinus venosus is the final collecting point of fetal venous circulation and develops into the posterior part of the right atrium, the sinoatrial node, and the coronary sinus.<sup>2</sup>

The primitive atrium develops into two separate atria. The primitive ventricle develops primarily into the left ventricle (LV) and the bulbus cordis forms part of the right ventricle. Septa form within the atria and ventricles to separate the left and right sides of the heart.<sup>2</sup>

The embryologic truncus arteriosus develops into the paired arterial trunks; the ascending aorta and pulmonary artery.<sup>3</sup>

Over the last decade, good quality of serial histological sections<sup>4</sup> and scaled reproductions of human embryos have been reported.<sup>5</sup>

On imaging, Preeta et al. showed human cardiac developmental process using high-resolution magnetic resonance imaging and episodic fluorescence imaging.<sup>6</sup>

Recently, progressive advances in medical ultrasonography, especially high-frequency transvaginal ultrasonography and the color Doppler equipment, allow access to the developing embryonic human heart.

Embryo crown-rump-length (CRL) at 2 mm shows a discernible heartbeat. At this time, the embryonic heart is in the cardiac tube

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stage. Embryo CRL at 5 mm shows distinct differential movements of the ventricles and atria (13th Carnegie stage, 6+4/7 gestational weeks). At the 7th gestational weeks, an interventricular septum can be visualized in the embryonic heart. Although a heartbeat can be detected and gross cardiac structures are visualized early in gestation, visualization of some embryologically important intracardiac structures, such as the endocardial cushion, atrioventricular foramen, or atrioventricular valves are still limited, even with the latest high-end equipment.

Cine function and color Doppler provide some valuable information about the morphology and function of the developing embryonic heart.

In scanning human embryos, safety issues should be kept in mind. Examination time should be kept as short as possible. Output levels should be kept as low as is reasonably achievable. Thermal and mechanical effects can be produced by diagnostic ultrasound. Mechanical effects have been demonstrated in tissues containing gas. However, the fetus does not produce or retain gas, mechanical effects are not a concern.

For the human embryo, a temperature elevation >1.5°C can be hazardous. Under temperature index (TI) <1.0, temperature elevation

in soft tissue (such as an embryo) caused by ultrasonographic examination with a usual Mode (2D, 3D) does not increase by  $>1.5^{\circ}\text{C}$ . However, narrow color box examination and concentrated pulsed-wave Doppler can cause temperature elevation  $>1.5^{\circ}\text{C}$  during a long examination time. For the evaluation of the embryonic heart using ultrasonography, keep the principle of "As Low As Reasonably Achievable" (ALARA) and the least use of color Doppler and pulsed Doppler should be applied in a short period of the examination time.

**CARNEGIE STAGE 9 (19–21 DAYS OF CONCEPTION, 5 GESTATIONAL WEEKS), CRL 2 MM**

**Morphologic Changes**

Paired endocardial tube.

The heart begins to develop near the head of the embryo (cardiogenic region).

The heart starts to beat and pump blood at around day 21 or 22.

**Ultrasonographic Findings**

The length of the embryo (green) is measured at 2.2 mm. The heart is a paired tube form (Fig. 2A). Heartbeat can be detected in an embryo measuring  $>$  over 2 mm. At this stage, the yolk sac (yellow ring) is much larger than the tiny embryo (green ring). The red dot is beating the cardiac tube.

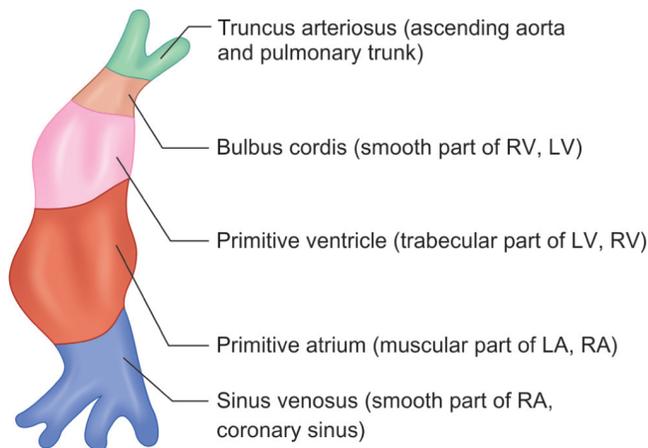


Fig. 1: Tubular heart

**CARNEGIE STAGE 10 (22–23 DAYS OF CONCEPTION, 5 WEEKS 1–3 DAY OF GESTATION), CRL 2.5 MM**

**Morphologic Changes**

Single primitive cardiac tube.

The two endocardial tubes descend into the thoracic cavity, where they begin to fuse into a single primitive cardiac tube. Cardiac tube fusion is complete at about 22 days.

The cardiac tube continues stretching and by day 23, cardiac looping begins.

**Ultrasonographic Findings**

The heart structure appears as a single beating echogenic dot.

**CARNEGIE STAGES 11–12 (23–26 DAYS OF CONCEPTION, 5 WEEKS 2–5 DAYS OF GESTATION), CRL 3–3.5 MM**

**Morphologic Changes**

Looping cardiac tube.

Cardiac tube looping is occurring inside the pericardial sac.

Neural crest cells migrate from rhombomere 6, 7 to pharyngeal arch 3.

**Ultrasonographic Findings**

In this ultrasound image, CRL is 3 mm and the heartbeat is more evident. Inside of the beating cardiac tube, a more echogenic thick region and a less echogenic thin region can be differentiated (Fig. 2B). The more echogenic region is presumably a primitive ventricle. At this stage, the heartbeat occurs simultaneously in the entire cardiac tube. The yellow ring is the yolk sac. Pink dot is looping cardiac tube (Fig. 3).

**CARNEGIE STAGE 13 (28 DAYS OF CONCEPTION, 6 WEEKS OF GESTATION) (9.5 DAYS OF RAT EMBRYO), CRL 4.5 MM**

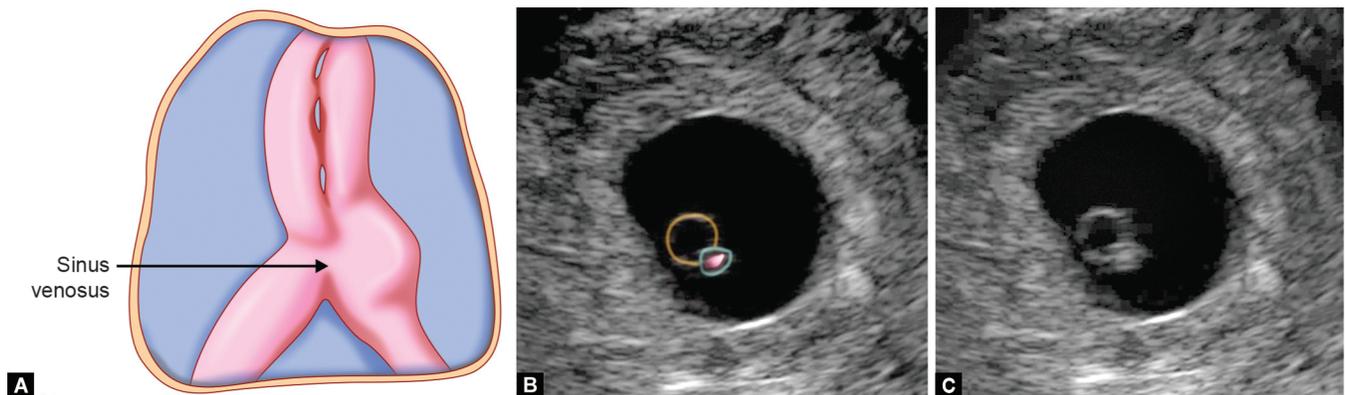
**Morphologic Changes**

Primitive ventricles and primitive atria.

Interventricular, interatrial septation budding.

Interventricular foramen.

Single undivided truncus arteriosus.



Figs 2A to C: Carnegie stage 9: (A) Schematic diagram; (B and C) Ultrasonographic findings

Primitive ventricles and primitive atria are discernible. Interventricular, interatrial septation starts. A common AV canal is present. The interventricular foramen is present. Truncus arteriosus is a single undivided state.

**Ultrasonographic Findings**

In this ultrasound image, CRL is 3 mm. The heart occupies nearly the whole thorax and protrudes ventrally (Figs 4C and D). Primitive ventricles (ventral thick region, pink-colored) and primitive atria (dorsal thin region, yellow-colored) are now discernible and cardiac contractions are divided into systolic and diastolic. Atrial size is larger than ventricular size. Pericardial effusion can be detected.

Due to trabeculation of the wall, the ventricle appears hyperechogenic and thicker than the atria (Figs 4A to D)

**CARNEGIE STAGE 14 (32 DAYS OF CONCEPTION, 6 WEEKS 4 DAYS OF GESTATION), 10 DAYS OF RAT EMBRYO, CRL 6 MM**

**Morphologic Changes**

Primitive endocardial cushion.

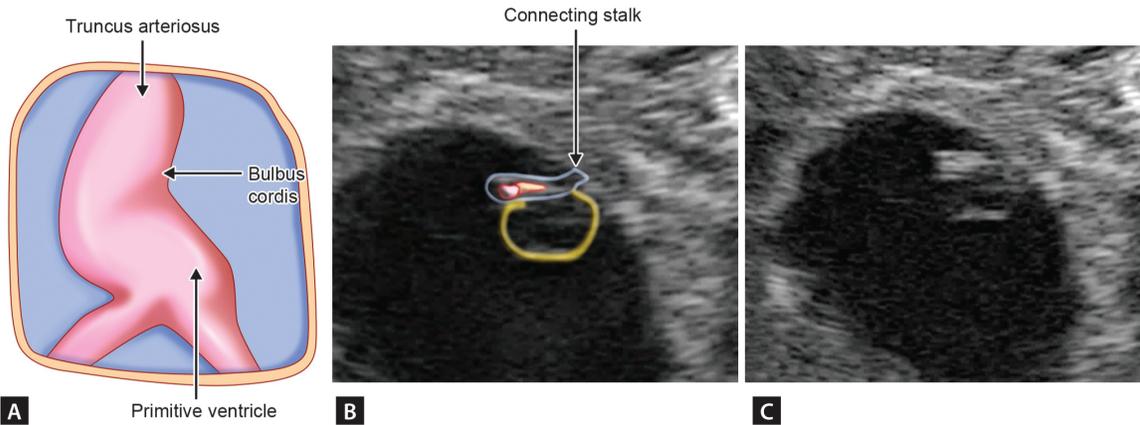
Atrial spine.

Septum primum.

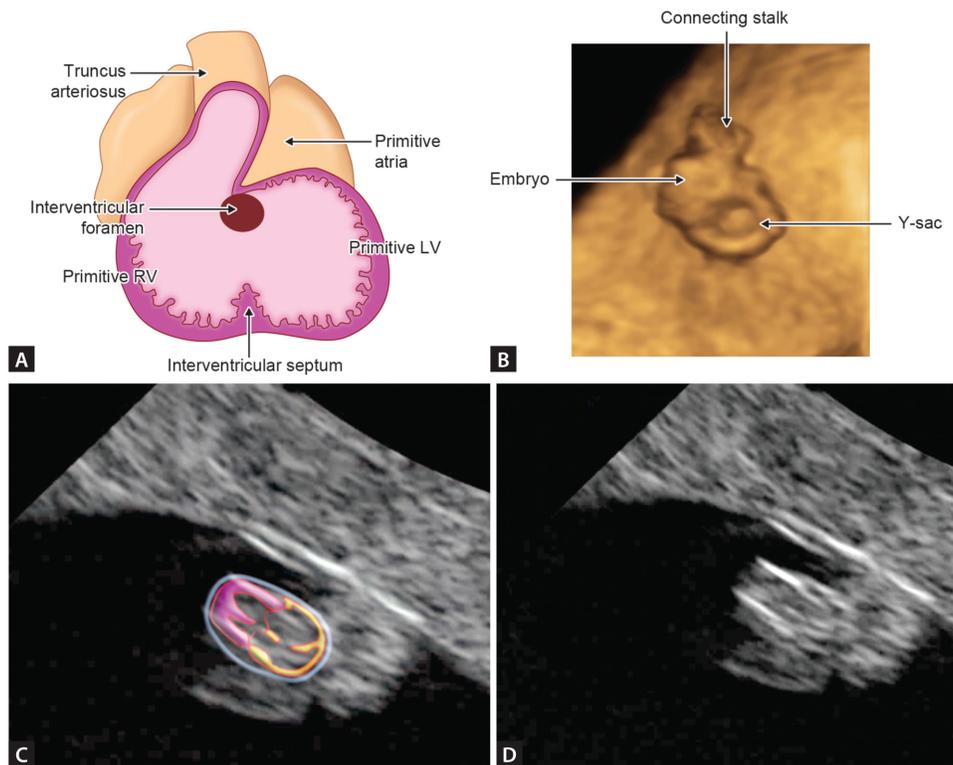
Atrioventricular canal.

At the end of the 6 weeks of gestation, primitive endocardial cushions appear.

Histologically, the atrial spine is observed at this stage and fuses with the inferior atrioventricular cushion. The septum primum can

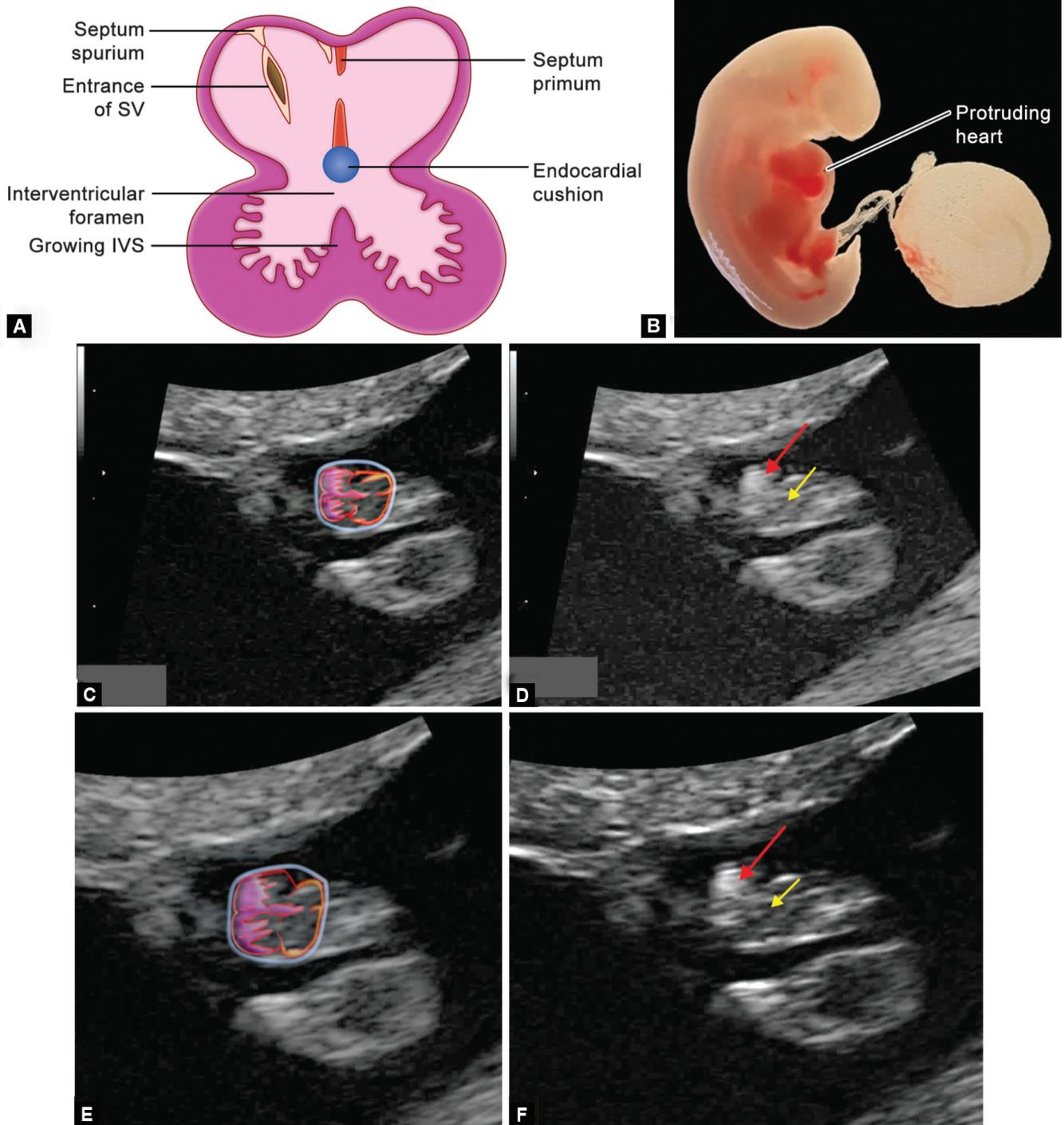


Figs 3A to C: Ultrasonographic findings of Carnegie stages 11–12

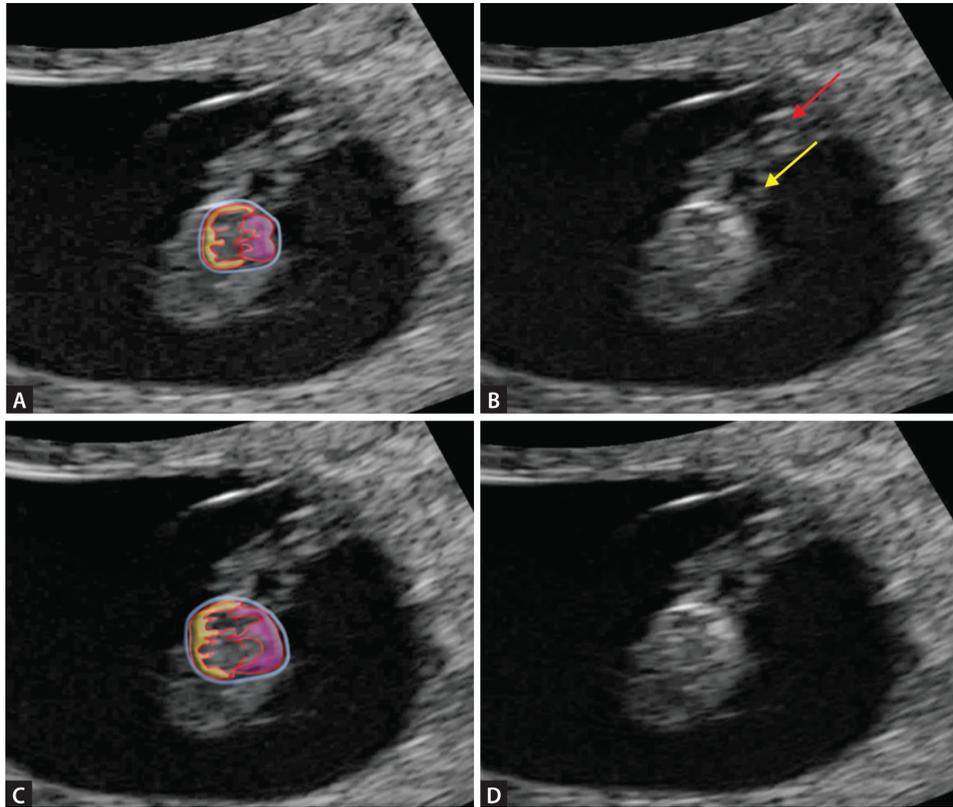


Figs 4A to D: Ultrasonographic findings of Carnegie stage 13





Figs 5A to F: (A) Sinus venosus; (B) Embryo (same developmental stage); (C and D) Systolic phase; (E and F) Diastolic phase



Figs 6A to D: (A and B) Systolic phase; (C and D) Diastolic phase

be observed at the end of the 6th week of gestation. Later, the septum secundum develops as an infolding of the dorsal wall of the right atrium.<sup>6</sup>

Large endocardial cushions are seen prominently at the center of the cardiac loop.

The atrioventricular canal is divided by the endocardial cushions.<sup>6</sup>

**CARNEGIE STAGE 15 (36 DAYS OF CONCEPTION, 7 WEEKS 1 DAY OF GESTATION), 11.5 DAYS OF RAT EMBRYO, CRL 8 MM**

**Morphologic Changes**

Large atria compare to ventricles.

- The LV is larger and thicker than the right ventricle.
- Ostium primum.
- Apposing atrioventricular endocardial cushion.
- Truncal cushion.

The atria are relatively large compared to the ventricles. Both right and left atria communicate through the ostium primum. The LV is larger and thicker than the right. The atrioventricular endocardial cushions are apposing.<sup>5</sup> The main cardiac walls are formed between days 27 and 37. Truncal cushions are observed in the form of swellings.<sup>6</sup>

**Ultrasonographic Findings**

Ventricles and atria are clearly differentiated on ultrasonography (Figs 5A to F). The heart appears as a mass protruding from the embryo. Left and right ventricles can be divided by an incomplete interventricular septum. The left ventricle shows a more thicker and brighter echo due to prominent ventricular wall trabeculations (upper chamber on Figures 5D and F, long red arrow). The endocardial cushion is located in the center of the heart (short yellow arrow)

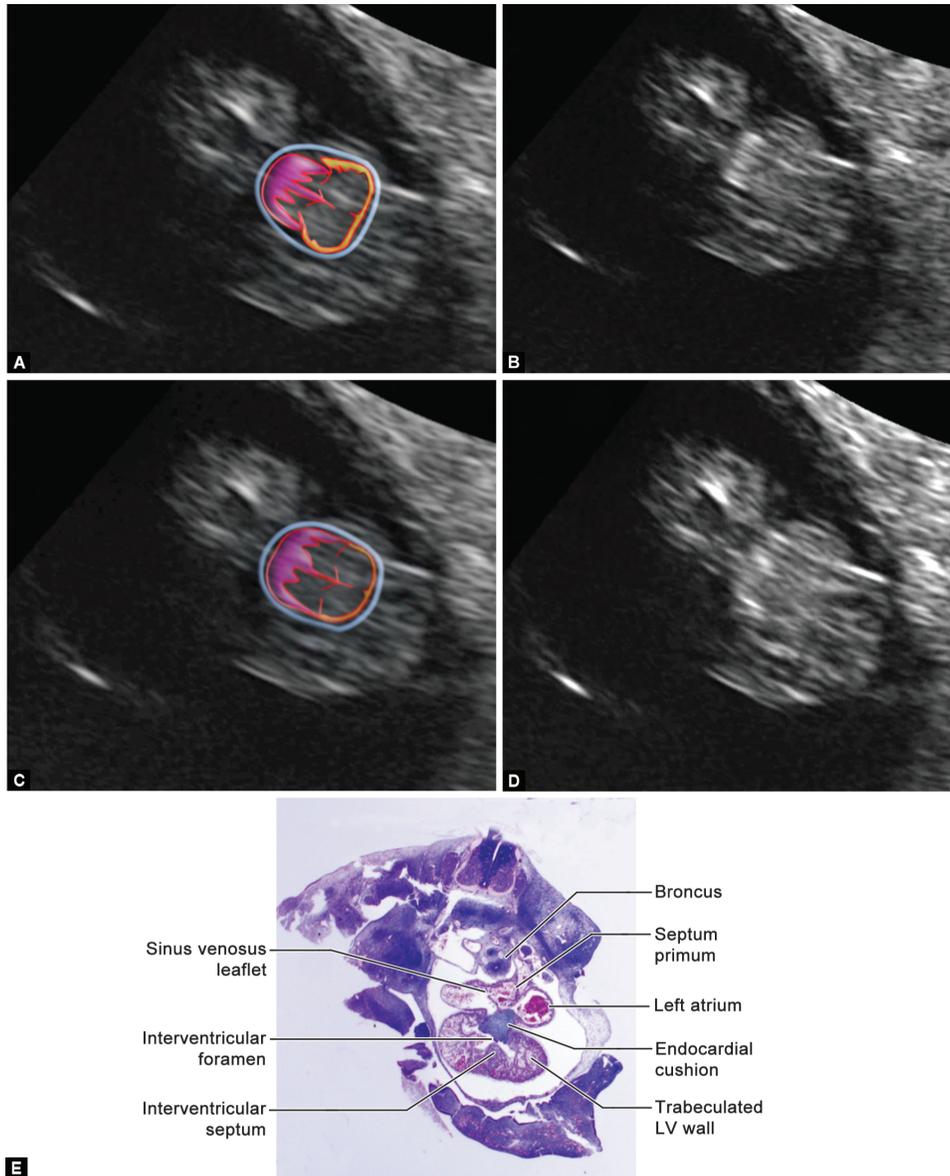
**CARNEGIE STAGE 16 (40 DAYS OF CONCEPTION, 7 WEEKS 6 DAYS OF GESTATION), CRL 10 MM**

**Morphologic Changes**

Separate right and left atrioventricular canals.

- Complete atrial septum primum.
- Vena caval valve.
- Interventricular foramen.
- Three-layered cardiac wall.

Atrioventricular endocardial cushions separate the right and left atrioventricular canals. Atrial septum primum is complete. The right horn of the venous sinus is incorporated into the right atrial wall and the venous valves are emerging.<sup>5</sup>



**Figs 7A to E:** (A and B) Systolic phase; (C and D) Diastolic phase; (E) Histologic section from rat embryo of same developmental stage (13 ED of rat); ED, embryonic day means post-conception day

The lower part of the ventricular myocardium develops into trabecular tissue.<sup>5</sup> Interventricular foramen persists. Atrial contraction time is shorter than ventricular contraction time.

The cardiac wall presents three layers: endocardium, myocardium, and epicardium.<sup>5</sup> Early outflow septation begins.

**Ultrasonographic Findings**

CRL of the embryo is 10 mm. Ventricles and atria are readily differentiated (Figs 6A to D). Ventricles are becoming hyperechoic and thicker as trabeculations of the ventricular wall evolve. The interventricular septum is detected, but interventricular foramen is not evident on ultrasonography. A long red arrow indicates umbilical cord and a short yellow arrow indicates allantoic cyst (Fig. 6B)

**CARNEGIE STAGE 17 (42 DAYS OF CONCEPTION, 8 WEEKS OF GESTATION), 12.5 DAYS IN THE RAT EMBRYO, CRL 11 MM**

**Morphologic Changes**

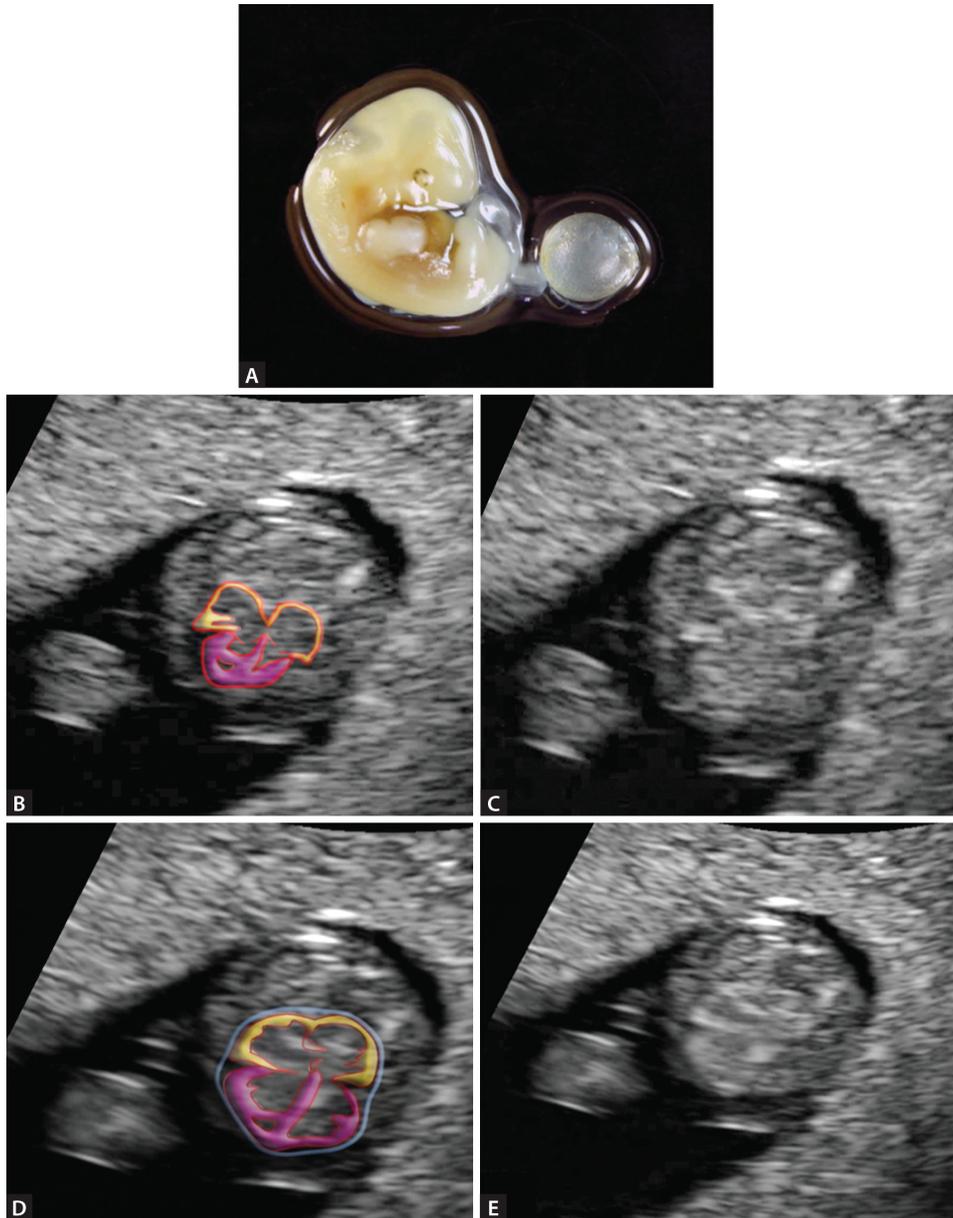
Ostium primum closed.

Separate AV canals.

Interventricular foramen.

Separation of Truncus arteriosus.

Ostium primum has been completely closed by the septum primum. The septum secundum starts to appear.<sup>5</sup> The atrioventricular canals are completely separated.



**Figs 8A to E:** (A) Embryo (CRL 20 mm); (B and C) Systolic phase; (D and E) Diastolic phase

Atrioventricular junction is developing, but interventricular foramen exists.

Truncus arteriosus is undergoing septation into the aorta and pulmonary artery, starting distally and extends proximally.<sup>2,7</sup>

**CARNEGIE STAGE 18 (44 DAYS OF CONCEPTION, 8 WEEKS 2 DAYS OF GESTATION), 13 DAYS IN THE RAT EMBRYO, CRL 13 MM**

**Morphologic Changes**

Complete muscular interventricular septum.

Ostium primum closed.

Endocardial cushion fusion.

Developing AV valves, semilunar valves.

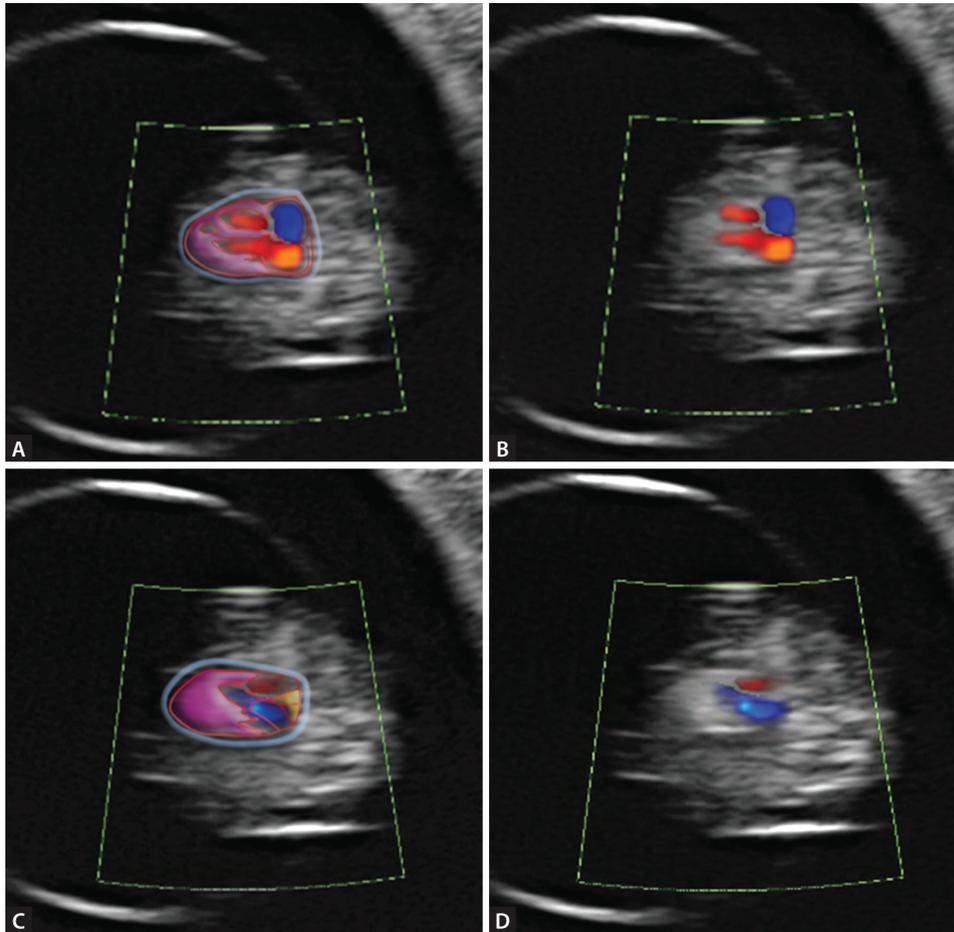
The interventricular septum is complete, but the interventricular foramen is still present.<sup>5</sup> Completion of muscular interventricular septum growth, but inlet ventricular septum is incomplete. Ostium primum is closed as septum primum attaches to the superior endocardial cushion.<sup>5</sup>

The tricuspid and mitral valves appear as small rounded prominence of reticular gelatinous tissue. The semilunar valves are distinguishable on the histologic section.<sup>5</sup>

Now, the heart is four-chambered organ.

**Ultrasonographic Findings**

Embryo length is 13 mm. Atrial size is larger than that of the ventricle. Small thick echogenic ventricles contracting on Figure 6B. Valve movements are not evident on ultrasonography (Fig. 7).



Figs 9A to D: (A and B) Four chamber planes (diastolic phase); (C and D) Four chamber planes (systolic phase);

**CARNEGIE STAGES 19–21 (48–52 DAYS OF CONCEPTION, 8 WEEKS 2–5 DAYS OF GESTATION), 13.5 ED IN THE RAT EMBRYO, CRL 16–23 MM**

**Morphologic Changes**

Complete interventricular septum.  
 Interventricular foramen closed.  
 Separate outflow tract (aorta and pulmonary trunk).  
 Membranous and inlet portion of the interventricular septum are complete and the interventricular foramen is closed.<sup>5</sup>  
 At the end of 8 weeks of gestation, separate aortic and pulmonary outflows were observed.<sup>8</sup>

**Ultrasonographic Findings**

Ultrasonographic images of CRL 19 mm embryo. Atria and ventricles are more readily discernible and four heart chambers are differentiated (Fig. 8).

CRL of this embryo is 22 mm. Blue flow indicated right ventricular outflow (pulmonary artery flow). Diastolic and systolic flows are clearly detected with the color Doppler ultrasound (Fig. 9).

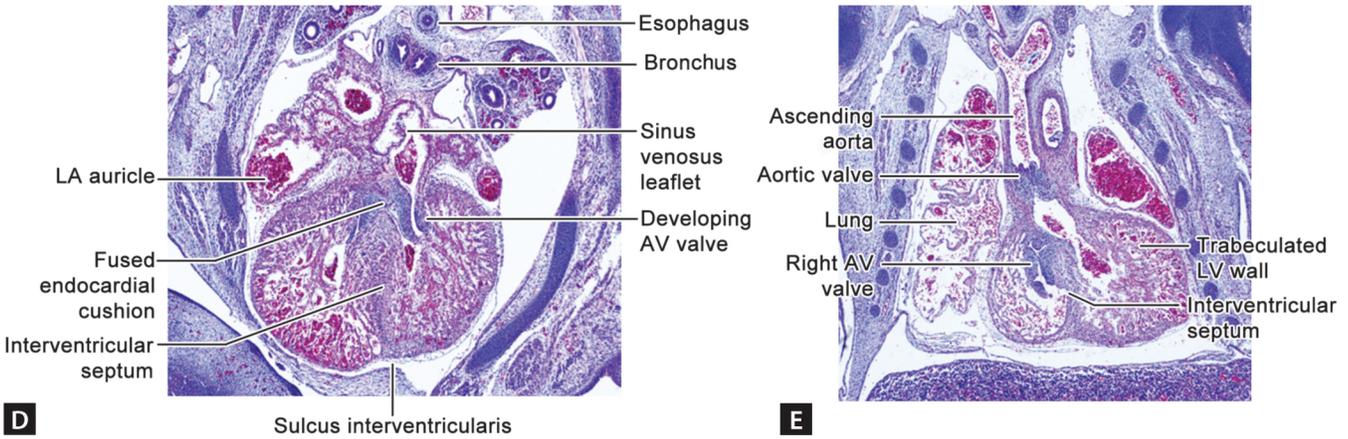
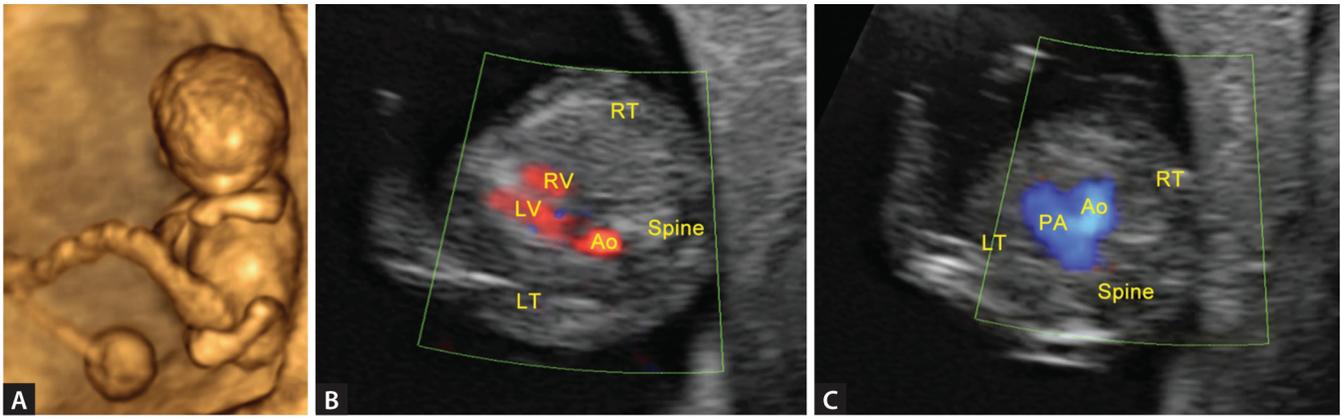
**CARNEGIE STAGE 22 (54 DAYS OF CONCEPTION, 9 WEEKS 1 DAY OF GESTATION), 14.5 ED IN THE RAT EMBRYO, CRL 26 MM**

**Morphologic Changes**

Complete interventricular septum.  
 Foramen ovale.  
 Coronary circulation.  
 All definite major cardiac structures identified.  
 The inlet and membranous portions of the ventricular septum are fully closed.<sup>6</sup>  
 Foramen ovale communicates the two atrial cavities.<sup>5</sup>  
 Coronary arteries with their main branches can be identified on histologic slides.<sup>5</sup>

**Ultrasonographic Findings (Fig. 10)**

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**D**

**E**

Estimated gestational age (weeks)	6 1/4	6 1/2	7 1/4	7 3/4	7 5/8	8	8 1/2	8 3/4	8 5/8	9 1/4	9 3/8
Carnegie stage	13	14	15	16	17	18	19	20	21	22	23
1. Cardiac loop	█										
2. Arterial septation		█									
• Septum primum		█									
• Septum secundum		█									
3. Interventricular foramen			█								
4. Ventricular septation			█								
• Muscular interventricular septum			█								
• Inlet interventricular septum										█	
• Outlet interventricular septum											█
5. Atrioventricular junction/valve formation											
• Mitral valve											
• Tricuspid valve											
6. Outflow septation			█								
7. Semilunar valve formation											
• Aortic valve											
• Pulmonary valve											

**F**

**Figs 10A to F:** (A) Image of the same embryonic stage; (B) Four-chamber heart; (C) Three-vessel view (diastolic phase); (D) Histologic section from rat embryo of the same developmental stage (14 ED of rat); (E) histologic section from rat embryo of same developmental stage (14 ED of rat); (F) The development time course of human cardiac morphogenesis. Redrawn from the *Figure of Circulation* 2009;120:343-51 (6)

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