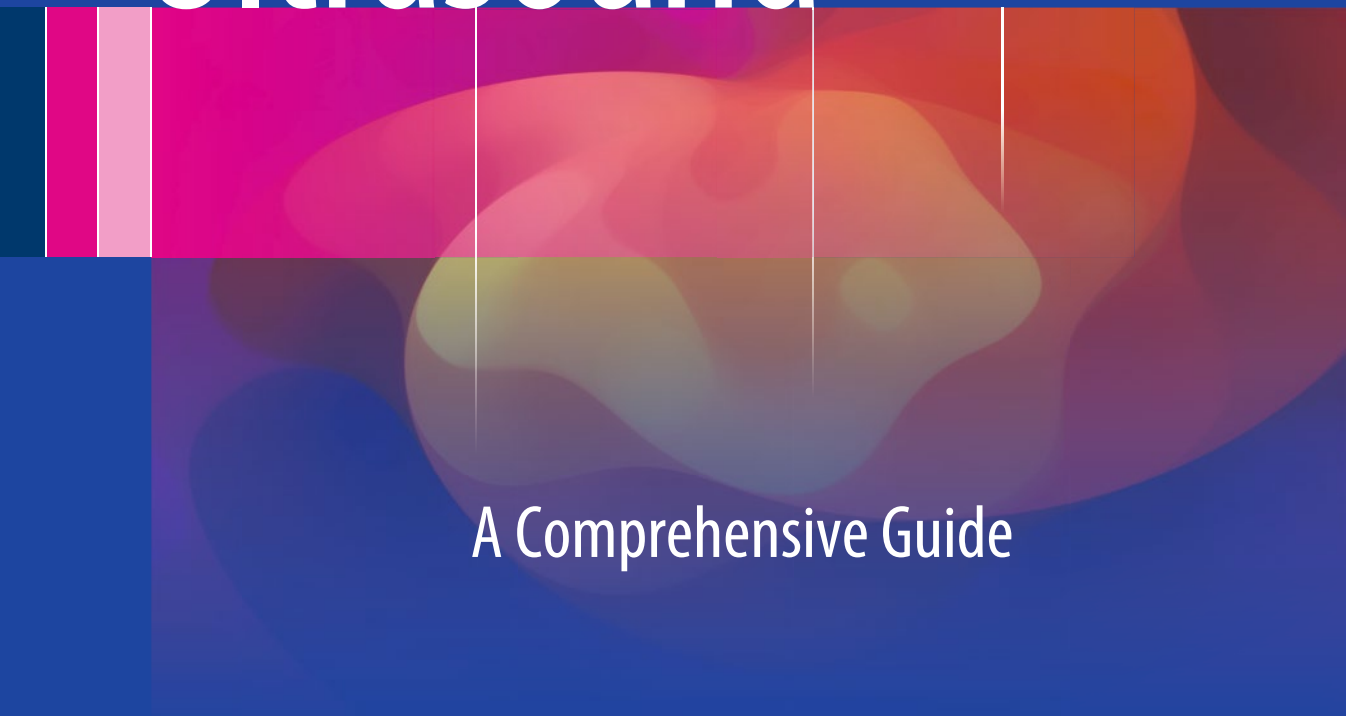
Jacques S. Abramowicz
Editor

First-Trimester Ultrasound



A Comprehensive Guide

Springer

First-Trimester Ultrasound

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Preface

There is, to our knowledge, no Ultrasound book dedicated exclusively to the first trimester of pregnancy. The present book, authored by, arguably, the best in their field, comes to fill this void. It is devoted to the early stages of pregnancy, normal and abnormal, including, among others, the period immediately preceding it, embryology notions, maternal diseases that can justify early scanning, elements of teratology, examination guidelines, normal anatomy and fetal anomalies, the fetal heart, multiple gestations, genetics concepts, new rules in the diagnosis of viable and ectopic gestations, gestational trophoblastic disease, invasive procedures and gynecological incidental findings, as well as chapters on the use of Doppler and three-dimensional ultrasound. The wonderful authors, rather than receiving strict limits, were given "literary freedom." Thus, there is inevitable overlap between chapters. I apologize to the reader, but, since it is safe to assume that most will not read this book cover to cover in a single session, each chapter is independent and will provide information about an entire and, sometimes, expanded topic. The number of healthcare professionals—physicians, sonographers, nurses—using ultrasound in obstetrics and gynecology is ever growing. A large number of specialties, from obstetrics and gynecology and maternal-fetal medicine to, naturally, radiology as well as emergency medicine and family medicine, employ this technology daily. It is hoped that this will be a reference for all these as well as for students, residents, and fellows in these various fields.

I am deeply grateful to all the authors for accepting to be part of this endeavor. Thank you to all the sonographers with whom I've worked over the years and to my patients and their babies who have taught me so much.

This book is dedicated to my parents, Sarah and Theo; my children, Shelly and Ory (and their spouses, Garrett and Esther); my grandchildren, Sarah and Noah-Theo; and mostly to my wife, Annie, my best friend, the love of my life.

Detroit, MI, USA — Jacques S. Abramowicz, MD

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Ultrasound in the First Trimester and Earlier: How to Keep It Safe

1

Jacques S. Abramowicz

"Ultrasound is safe. Ultrasound is not X-rays. Our machines are FDA-approved." These are the statements most commonly made when initiating a conversation on safety of ultrasound. This is one of the reasons cited for its becoming an essential tool in medicine (together with its relatively low cost and immediate results availability). Diagnostic ultrasound (DUS) has been in use for over half a century in obstetrics and gynecology [1] and the benefits of this technology are multiple [2]. Most pregnant women have 2–3 ultrasound examinations (and many more in certain countries) during their pregnancies. In early pregnancy and before (i.e., in Artificial Reproductive Technologies [(ART]), these include serial scans of the developing follicles during ovulation induction [3] and in the earliest stages of gestation [4], first-trimester ultrasound for viability and/or aneuploidy screening (nuchal translucency, NT) and, more and more, early anatomy survey [5]. Such is the widespread enthusiasm and the generally accepted notion of safety that its use has spilled into the commercial world with mall stores offering non-medical ultrasound or "souvenir" scans. The record of safety of DUS is excellent: there are no epidemiological studies demonstrating harmful effects in human fetuses [6]. Most human epidemiological studies, however, published so far are based on information obtained with pre-1991/1992 machines. Around that time, the US Federal Drug Administration (FDA) allowed the acoustic output of ultrasound machines for fetal use to be increased from 94 to 720 mW/cm^2, a factor of almost 8 [7, 8]. Is there enough evidence to validate the use of ultrasound imaging in general and Doppler in particular in the first trimester [9] and could ultrasound have detrimental effects on the fetus in the first trimester, a time of maximal susceptibility to external factors? If there are clinical indications to perform these scans (and if there were none, there would be no raison-d'être for this book) safety must be guaranteed by educating the end-users on ways to limit the possible hazards of exposure of the follicles/ova and the fetus at early stages of gestation [2].

Bioeffects of Ultrasound

Ultrasound is a waveform with a succession of positive and negative pressures [10]. Whenever an ultrasound beam traverses biological tissues, two major mechanisms are operative: thermal and non-thermal (also known as mechanical). This will occur *every time* ultrasound is used. As the waveform travels through tissue, it loses amplitude by absorption and scatter. With absorption, energy is converted into heat, hence a thermal effect [11], an indirect effect of the

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waveform. A direct effect of the passage of the waveform, secondary to the succession of positive and negative pressures is non-thermal or mechanical [12].

Thermal Effects

Human body normal core temperature is generally accepted to be 37 °C with a diurnal variation of ±0.5–1 °C [12]. Temperature in the human fetus is slightly higher than maternal body temperature by 0.3–0.5 °C during the early gestation (two first trimesters). During the third trimester fetal temperature is higher by 0.5 °C than that of its mother. Ultrasound may cause a rise in temperature in insonated tissues [13]. This rise will be small and, most likely, clinically insignificant, *if certain precautions are respected* (as detailed below). Why is this important? Because specific structural abnormalities have been shown to be produced by increased temperature in many pregnant animal studies, as well as several controlled human studies [14], *but not by ultrasound*. Elevated maternal temperature in early gestation, secondary to viral infection, for instance, has been associated with a higher than expected incidence of congenital anomalies [15]. Edwards and others have demonstrated that hyperthermia is teratogenic for many animal species (such as guinea pigs, rats, monkeys, and more), including the human [14, 16]. Major anomalies observed included microcephaly, encephalocele, microphthalmia, skeletal anomalies as well as growth delay. It was suggested that a 1.5 °C temperature elevation above the normal body temperature should be considered a universal threshold [17]. The acceptance of a threshold forms the basis for the ALARA (As Low As Reasonably Achievable) principle: keep the exposure as low as possible, for the least amount of time possible, but yet enough to get adequate diagnostic images [18]. Some scientists, however, assert that a*ny* temperature increment for *any* period of time has *some* effect, the higher the temperature differential or the longer the temperature increment the greater the likelihood of producing an effect, i.e., there is no thermal threshold for hyperthermia-induced birth defects [19, 20]. Whether a threshold exists or not, two facts are undeniable: ultrasound has the potential to elevate the temperature of the tissues being scanned [21–24] and elevated maternal temperature, whether from illness or exposure to heat, can produce teratologic effects [14, 25–27]. Consequently, the obvious question that emerges is: can diagnostic ultrasound produce harmful/teratological temperature rise in the fetus [11, 22, 28]? Some believe that such a temperature rise is, in effect, the major operational mechanism for ultrasound bioeffects [12, 29]. For prolonged exposures, temperature elevations of up to 5 °C have been obtained [28]. The actual in situ temperature change in insonated tissues depends on the balance between heat production and heat loss. Local perfusion is a specific tissue condition that strongly influences the amount of heat loss and which very clearly diminishes the risk, if present. In early pregnancy, under 6–8 weeks, there appears to be minimal maternal–fetal circulation and minimal fetal perfusion, which may potentially reduce heat dispersion [30]. Only at about weeks 10–11 does the embryonic circulation actually link up with the maternal circulation [31]. The early absence of perfusion may thus lead to some underestimation of the actual ultrasound-induced temperature in early gestation. Interestingly, this lack of perfusion, which also exists in the eye, is one reason why the spatial-peak temporal-average intensity (I_{SPTA}) for ophthalmic applications has been kept very low, in fact, much lower than peripheral, vascular, cardiovascular, and even obstetric scanning, despite the general increase in acoustic power that was allowed after 1992 (Table 1.1). One should note that there are some similarities

Table 1.1 Changes over the years in I_{SPTA} (in mW/cm^2) in various medical applications[a]

Ultrasound clinical application	1976	1986	1991
Ophthalmic	17	17	50
Fetal, neonatal, pediatric imaging	46	94	720
Cardiac (adult)	430	430	720
Peripheral vascular	720	720	720

[a]Adapted from various sources [8, 12, 59, 166, 170]

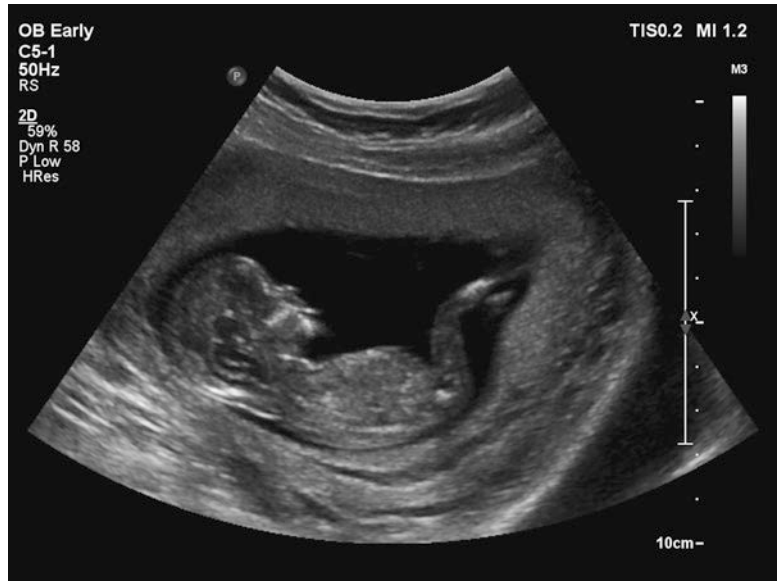

Fig. 1.1 In early pregnancy the entire fetus is within the ultrasound beam. Gestational age of 12 weeks

in physical characteristics between the early, first-trimester embryo and the eye: neither is perfused; they can be of similar size; and protein is present (in an increasing proportion in the fetus). At about gestational weeks 4–5, the gestational sac is about the size of the eye (2.5 cm in diameter), and by week 8, it is around 8 cm in diameter [32]. Ultrasound imaging in these early stages of gestation involves "whole body" scanning since the fetal size is less than the cross section of the beam (Fig. 1.1). An additional factor, virtually ignored clinically, is modifications of tissue temperature due to ambient maternal and fetal temperatures. Elevated maternal temperature is immediately translated into a similar increase in the fetus which may compound the ultrasound-induced heat burden [33]. On the other hand, motions (even very small) of the examiner's hand as well as the patient's breathing and body movements (in the case of obstetric ultrasound, both the mother's and the fetus') tend to spread the region being heated. However, for spectral (pulsed) Doppler studies, conditions may be different (see below). As mentioned above, there is a mathematical/physical relation between temperature elevation and several beam characteristics. The elevation is proportional to the product of the wave amplitude, length of the pulse and pulse-repetition frequency (PRF). Hence, manipulating any of these via instrument controls will alter the in situ conditions. Temperature increases of 1 °C are easily reached in routine scanning [34]. A general threshold of temperature elevation of 1.5–2 °C has been suggested before any evidence of developmental effect occurs [12]. An increase of 2.5 °C and above is possible with 1 h of exposure to ultrasound [12]. When using an abdominal probe, the skin surface is close to room temperature and heat is removed by air convection but in the case of endovaginal scanning, tissues are at an average temperature of 37 °C—or possibly higher in febrile patients—and there is very little heat removal [35]. In addition, the surface of all ultrasound transducers, including endovaginal probes, self-heats [36], and particular attention is necessary during ART procedures and the first 10–12 weeks of gestation, when endovaginal scanning is often the favored method. As was concluded by the World Federation for Ultrasound in Medicine and Biology (WFUMB), exposure that produces a maximum temperature elevation of no more than 1.5 °C above normal physiological levels may be used without reservation on thermal ground [37].

Non-thermal Effects

Ultrasound bioeffects may also occur through non-thermal or mechanical processes [38, 39]. These include acoustic cavitation, *if gas bubbles are present*, as well as radiation torque and force and acoustic streaming secondary to propagation of the ultrasound waves. Included in this category are physical (shock wave) or chemical (release of free radicals) effects. Bubble cavitation seems to be the major factor in mechanical effects [40, 41], as it has been demonstrated to occur in living tissues when insonated [42, 43]. Non-thermal mechanisms have been implicated in biological effects of ultrasound in animals, such as local intestinal [44], renal [45], and pulmonary hemorrhages [46], although cavitation could not always be incriminated. Furthermore, since there does not seem to be gas bubbles in the ovarian vasculature or parenchyma, nor the fetal lungs or bowels (where effects have been described in neonates or adult animals), the risk to the ovum and fetus from mechanical effect appears to be minimal [47]. However, the use of contrast agents (including agitated saline) to image the fallopian tubes or the endometrial cavity for instance, introduces these potential cavitation foci [48]. Details on the cavitation phenomenon can be found in various publications [38, 40, 43, 49, 50]. Another described result of mechanical energy is hemolysis [51]. Again, it is evident, however, that the presence of some cavitation nuclei is necessary for hemolysis to occur. In the presence of such contrast agents, fetal red blood cells are more susceptible to lysis from ultrasound exposure in vitro [52]. In addition to the above, fetal stimulation caused by ultrasound (Doppler) insonation has been described, with no apparent relation to cavitation [53]. This effect may be secondary to radiation forces associated with ultrasound exposures. These forces were suspected at the earliest stages of ultrasound research [54] and are known to possibly stimulate auditory [55] and other sensory tissues [56]. The main effects of non-thermal damage have been demonstrated in mammalian tissues containing gas where capillary bleeding has been observed [39, 42, 57]. This potentially pertains to the neonatal lung, intestine and also, as noted above, in the presence of ultrasound microbubble contrast agents. Several non-thermal mechanisms, not related to cavitation have also been described: radiation force, acoustic streaming, modification of electrical potentials, effect on cardiac performance and stimulation of bone repair [12]. None of these have been demonstrated in humans and no harmful effects of diagnostic ultrasound, secondary to non-thermal mechanisms have been reported in human fetuses.

The Output Display Standard (OSD)

Until 1992 acoustic outputs of clinical ultrasound machines had specific limits. For instance, the upper limit of the spatial peak temporal average intensity or I_{SPTA} (the most clinically useful intensity used to determine acoustic power of the ultrasound beam) for adult use was 720 mW/cm^2 and for fetal use, 94 mW/cm^2, which in fact, already had been increased from a previous maximum value of 46 mW/cm^2. It was assumed that higher outputs would generate better images and, thus, improve diagnostic accuracy. Hence, end-users required ultrasound manufacturers to increase their machines output. Some worry, however, was expressed regarding the actual amount of energy absorbed by a human fetus during an ultrasound examination. This amount cannot be measured precisely. Not only the lack of an internal recording device is a major issue but, in addition, elements such as variations in maternal body habitus, fetal position changes, and gestational age progression render such a task impossible. To allow clinical users of ultrasound to use their instruments at higher powers than originally intended and to reflect the two major potential biological consequences of ultrasound (thermal and mechanical), the American Institute of Ultrasound in Medicine (AIUM), the National Electrical Manufacturers' Association (NEMA) and the US food and Drug Administration (FDA), with representatives from the Canadian Health Protection Branch, the National Council on Radiation Protection and Measurements (NCRP) and 14 other medical organizations developed a

standard related to the potential for ultrasound bioeffects [12]. The Standard for Real-Time Display of Thermal and Mechanical Indices on Diagnostic Ultrasound Equipment, generally known as the Output Display Standard or ODS, was an attempt to provide quantitative safety-related information. This information was to appear on-screen during an exam, so that the end-users would be able to see how manipulation of the instrument controls during an examination causes alterations in the output and, thus, on the exposure, providing, from a clinical standpoint, a rough estimate to compare various modes of examination. As a consequence, the acoustic output for fetal use, as expressed by the I_{SPTA} went from a previous value of 94–720 mW/cm^2 (see Table 1.1). It is interesting to observe from the table that, for fetal imaging, the I_{SPTA} was allowed to increase by a factor of almost 16 from 1976 to the most recent values in 1992; yet virtually all epidemiological information available regarding fetal effects predates 1992. A further remarkable fact is that intensity for ophthalmic examination was increased from the original 17–50 mW/cm^2, a value approximately 12 times lower than the present allowed maximal value for fetal scanning. Furthermore, the clinical categories included in the analysis consisted of ophthalmic, fetal (without specification of gestational age), cardiac, and peripheral vascular examinations. Pelvic imaging (abdominal or transvaginal), including, naturally, examination of ovaries in ovulation induction, is not mentioned. The indices to appear on-screen (Fig. 1.2) were the thermal index (TI), to provide some indication of potential temperature increase and the mechanical index (MI), to provide indication of potential for non-thermal (i.e., mechanical) effects [58, 59]. The TI calculation is based on the formula:

$$\mathrm{TI} = W / W_{\mathrm{deg}}$$

where W is the acoustic power while scanning and W_{deg} is the acoustic power required to achieve an increase in temperature of 1 °C under similar conditions [60]. The TI has three variants [35]: TI for soft tissue ($\mathrm{TI_S}$), to be used mostly in early pregnancy when ossification is low (as well as in ART for ovulation studies), for bones ($\mathrm{TI_B}$), to be used when the ultrasound beam impinges on bone, at or near the beam focus, such as late second and third trimesters of pregnancy and for transcranial studies ($\mathrm{TI_C}$) when the transducer is essentially against bone, mostly for examinations in adult patients. These indices were required to be displayed if equal to or over 0.4. It needs to be made very clear that *TI does not represent an actual or an assumed temperature increase*. It bears some correlation with temperature rise in degrees Celsius, but in no way allowing an estimate or a guess as to what that temperature change *actually* is in the tissue. The TI represents reasonable "worst-case" estimate of the temperature rise resulting from the exposure. It can, thus, be used to assess the potential for harm via a thermal mechanism, the higher the TI, the higher this potential. Calculations are also on the ultimate temperature reached after prolonged exposure. This time will be short (less than 5 min) with a narrow beam and good tissue perfusion, as is the case in late first-trimester scanning. When bone is present, this time is very short, approximately 30 s. An important point to remember is that experimental data has clearly demonstrated that this worst-case elevation of temperature may be a gross underestimation, by as much as a factor of 2 or even 6, and, more rarely, an overestimation [12]. Furthermore, exposure

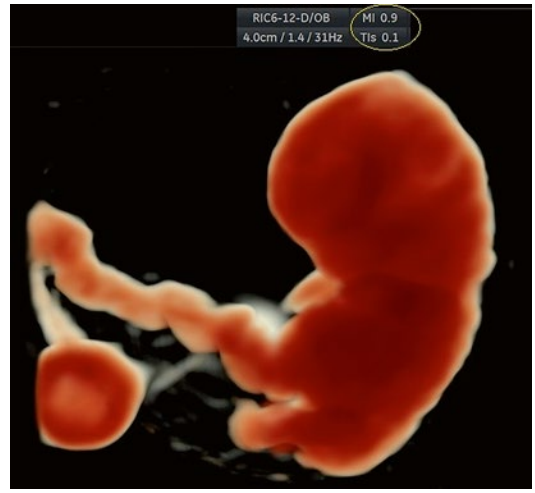

Fig. 1.2 The TI and MI acoustic indices as demonstrated on the monitor screen during routine ultrasound examination. In this picture, the MI is 0.9 and the $\mathrm{TI_S}$, 0.1

time is not part of the equation, nor is it in the second index, the MI, which represents the potential for cavitation in tissues, but is not based on actual in situ measurements. The MI is defined as:

$$\mathrm{MI} = p / \sqrt{f}$$

It is a theoretical formulation of the ratio of the peak rarefaction pressure to the square root of the ultrasound frequency (hence, the higher the frequency, the lesser risk of mechanical effect, which is an advantage in endovaginal scanning). As for the TI, exposure time is not part of the calculation. Both the TI and MI can and should be followed as an indication of change in output during the clinical examination. A major component of the implementation of the ODs was supposed to be education of the end-user. Unfortunately, this aspect of the ODS does not seem to have succeeded as end-users' knowledge of bioeffects, safety, and output indices is lacking. Both in Europe [61] and the USA [62], approximately 70 % of clinicians (physicians and sonographers, including nurses who perform ultrasound) show very poor, or no knowledge of bioeffects and safety issues, do not know what TI and MI represent and do not even know that these appear on-screen during clinical ultrasound examinations. This is true in several other countries [63–65] as well as among residents/fellows [66] and sonographers, regardless of their seniority [67]. Furthermore, several assumptions were made when formulating the indices, which bring questions on their clinical value [68]. Details can be found in the NCRP report 140 [12]. These indices, however, are the best mean we have, nowadays, to estimate, in real time, changes occurring in acoustic output of the instrument, although various modifications have been offered, in particular in regard to exposure time [69, 70]. There is, in fact, little information on energy output and exposure in clinical obstetrical ultrasound. Only relatively recently has it been shown that, if one considers TI and MI to be some indication of acoustic output, then the levels are low in the first [71, 72], second and third trimesters [73], and even Doppler studies [74]—although higher levels of TI can be reached in this modality—as well as 3D/4D examinations [75]. It should also be noted that in some countries, the number of prenatal ultrasound examinations has reached 10 per pregnancy and it is presently unknown whether there is a cumulative dose effect to exposure [76].

Ultrasound and the Ovum

Ultrasound has permeated the field of infertility and reproductive endocrinology, from diagnosing uterine anomalies [77], following development of the follicle [78], evaluating tubal patency [79], to its use in embryo transfer [80]. A study from 1982 demonstrated premature ovulation in women who underwent ultrasound examination of the ovaries (B-mode) in the late follicular phase [81]. The authors compared patients in induced ovulation cycles, followed by ultrasound (study group) or only by hormone levels (control group). They investigated timing of follicle rupture after the onset of LH surge or administration of hCG. Rupture never occurred before the 37th hour in control patients (no ultrasound in the follicular phase). However, (premature) ovulation was observed at 26–36 h in about 50 % cases in the study group (ultrasound during the previous 3 days or in the 36 h immediately following the ovulatory stimulus). This study was very concerning but has never been reproduced. Ultrasound-guided oocyte aspiration for in vitro fertilization and embryo transfer was reported in the early 1980s [82, 83]. It has now become routine [84]. There are only a few, relatively dated, studies aimed at determining the interaction between ultrasound exposure and successful fertilization. Most are, in fact, concerned with success or lack thereof of the procedure in terms of pregnancy rates and not possible bioeffects. Some researchers have reported deleterious effects of ultrasound on the menstrual cycle, particularly decrease in ovulation rates in mice [85] and premature ovulation [81], as well as reduced cumulative pregnancy rates in mice [86] and in humans [87]. Others have demonstrated no effects on the ovulation process or egg quality, including DNA and RNA synthesis [88], or on fertilization rate and embryonic development

following in vitro fertilization and embryo transfer [89]. In general, the clinically available data on ultrasound exposure of oocytes during meiosis are confusing. Some researchers reported a deleterious effect on the fertility of patients undergoing artificial insemination with a reduction in the cumulative rate of pregnancy [87]. A study of ultrasound exposure of meiotically active, preovulatory oocytes showed no differences between rats exposed to ultrasound after the LH surge and controls in terms of pregnancy rate, number of corpora lutea, implantations, pups, and mean pup and placental weights at autopsy on day 22 of pregnancy [90]. Others have claimed an increase in the success rate, allowing ultrasound monitoring of follicular growth [91], although, evidently, this is not a direct effect of ultrasound but of improved intervention timing. An attempt to clarify this was described by Mahadevan and colleagues [89]. They wanted to determine how oocytes obtained under ultrasound guidance affected the pregnancy rate. The results obtained with 3.5-MHz probes suggest that exposure of human oocytes to ultrasonic waves during the different phases of meiosis does not significantly influence the developmental potential of the in vitro fertilized embryos. Unfortunately, no researcher describes any of the relevant exposure parameters discussed earlier, except for ultrasound frequency.

Ultrasound in Early Gestation

There are many valid medical indications to perform ultrasound in early gestation [2, 92]. These are described in various parts of this book and include, among others, pregnancy location, accurate gestation dating, confirmation of viability, verification of number of fetuses, and early anatomy survey. All of these examinations are, generally, performed with B-mode, a mode with relatively low acoustic output. However, more recently, screening for genetic abnormalities, such as NT and early assessment of structural abnormalities are described in the literature in early (11–15 weeks) pregnancy [5, 93, 94]. While most of these are also performed with B-mode, often Doppler is used to detect blood vessels and/or to visualize and analyze cardiac valves [95], exposing the fetus to much higher energy levels (see below]. One needs to keep in mind that, even with B-mode, dwell time is important since prolonged examination can result in higher exposure levels [96]. Interesting, somewhat worrying and unexplained data have been published on an increased incidence of fetal anomalies in fetuses resulting from ART [97, 98]. Some concerning effects on the chorionic villi in women who had transvaginal ultrasound during the first trimester were reported [99]. There was a time–effect relation with activation of an enzyme pathway responsible for apoptosis through a mitochondrial pathway with exposures of 20 and 30 min but not 0 (control group) or 10 min.

Fetal Susceptibility to External Insults

The growing fetus is very sensitive to external influences. This is especially true in the first 10–12 weeks of gestation [100, 101]. Known teratological agents include, for instance, certain medications or drug of abuse taken by the pregnant woman, exposure to X-rays and elevated temperature, secondary to infectious diseases [102]. Gestational age is thus a vital factor when considering possible bioeffects: milder exposure during the preimplantation period or more severe exposures during embryonic and fetal development can have similar results and can result in embryonic/fetal death and abortion or a wide range of structural and functional defects. Most at risk is the central nervous system (CNS), due to a lack of compensatory growth of undamaged neuroblasts. In experimental animals the most common defects are of the neural tube as well as microphthalmia, cataract, and microencephaly, with associated functional and behavioral problems [14]. Other prominent defects are seen in craniofacial development, such as facial clefts [103], the skeleton [104], the body wall, teeth, and heart [105]. Hyperthermia in utero [due to maternal influenza for instance] was long known to potentially

induce structural anomalies in the fetus [106–108] but it has been described also as an environmental risk factor for psychological/behavioral disturbances [109] and, more particularly, schizophrenia [107]. It is stressed that these are not ultrasound-induced hyperthermia effects. Yet ultrasound has been shown to induce temperature increase in vivo [11, 21, 24, 29, 110–112], albeit not in humans. Subtle effects are possible, such as abnormal neuronal migration with unclear potential results [113]. One specific single specific effect has been described in various publications: a mild increase in the prevalence of non-right handedness among male children exposed to prenatal ultrasound with no other neurological, intellectual, behavioral, or physical anomalies [114–116]. Ultrasound has been implicated, in chicks who were insonated in ovo, in learning and memory disturbances [117]. A study failed to demonstrate a relation between ultrasound insonation in utero and decreased intellectual performance [118]. In mice, the etiology of symptoms similar to those seen in autism was attributed to ultrasound [119]. Extrapolation to humans is not automatic, despite the argument, by some, that the increased incidence of this condition in children over the last 20 years or so is secondary to the similar increase in the use of ultrasound in obstetrics [120]. One study reported on approximately 750 children, half with autism spectrum disorders and half without [121]. The conclusion was that ultrasound in any of the three trimesters of pregnancy could not be correlated with an increased risk of ASD. In fact, there is a serious lack of data examining the role of ultrasound in the etiology of autism while rigorously excluding other confounding factors [122]. If one, however, considers together the facts that hyperthermia is potentially harmful to the fetus and that ultrasound may, under certain circumstances elevate tissue temperature, then precaution has to be recommended, particularly in early gestation and especially with modes known to emit higher acoustic energy levels (such as pulsed Doppler).

Is Doppler Different and Can It Have Detrimental Effects on the Fetus in the First Trimester?

Ultrasound modalities can result in either scanned or unscanned exposure. Scanned conditions are associated with grey-scale B-mode images (the most commonly used real-time application), and Doppler images of tissue cross sections. Unscanned conditions are used for M-mode and pulsed-Doppler studies of tissue movement (such as cardiac valves) or blood velocity waveforms. This is clinically very important because for unscanned beams the power is limited to the area of the beam cross section, often very narrow (1 mm^2) in the focal region. For scanned beams the acoustic power is not limited to a narrow area, but may cover large areas in the lateral direction, hence less risk of high exposure at a specific point. Furthermore, a variety of movements intervene during B-mode imaging, such as fetal body motion, observer's hand movements, and maternal breathing. During a Doppler examination, however, it is necessary to have the transducer as steady as possible. This is because, in general, blood vessels or heart valves are small in comparison to the general organ or body size being scanned and even small movements will have more undesired effects on the resulting image. As described below, the most commonly used intensity (spatial peak temporal average intensity, I_{SPTA}) associated with Doppler ultrasound is the highest of all the general-use categories, 1180 mW/cm^2 for pulsed Doppler, as opposed to 34 mW/cm^2 for B-mode, a 35-fold difference. Dwell time (duration of exposure) is also of major importance: Ziskin [123] reported that among 15,973 Doppler ultrasound examinations, the average duration was 27 min (and the longest 4 h!). A study in chicken seemed to clearly implicate Doppler [117]. Chicken eggs were insonated on day 19- of a 21-day incubation period. Exposure was to B-mode for 5 or 10 min or to pulsed Doppler for 1–5 min. Eggs were allowed to hatch and learning and memory tests were performed in the chicks on day 2. Impairment in

ability to learn or in short, medium and long-term memory was not observed after B-mode exposure but was clearly demonstrated for those exposed to Doppler, with a dose–effect relationship. Furthermore, the chicks were still unable to learn with a second training session 5 min after completion of the initial testing. Hearing the fetal heart beat is certainly a very satisfying experience for the expecting parents. Often this is accomplished by using pulsed Doppler. This is so engrained in the minds of the public that each time ultrasound is mentioned in a television series or a movie, one can hear the heart beat in the background although the image on-screen is only of a B-mode exam. In fact, using Doppler to "listen" to the fetal heart is not new [124, 125]. This should be discouraged and replaced by M-mode assessment. If Doppler is used, it is sufficient to "hear" 3–4 heart beats and thus limit the exposure [126, 127]. One of the major uses of ultrasound is the prenatal detection of fetal abnormalities. The organ most commonly affected by major genetic disorders is the heart, and hence, extensive research is conducted in imaging and functional assessment of the heart. While B-mode is used to assess structure, Doppler (pulsed [spectral] and color) are the ideal techniques to examine heart function. A vast amount of literature has been published on the value of ultrasound examination of the fetal heart, using various techniques, including Doppler analysis of flow across the cardiac valves and Doppler velocimetry of various fetal vessels [128–130]. The vast majority of published reports was, until recently, on B-mode examinations around 18–20 weeks. However, several authors have demonstrated the feasibility of examining the heart much sooner in pregnancy, beginning around 10 or 11 weeks [131–134]. Doppler analysis has long been a tool to study cardiac function, although mostly in the placenta, umbilical or uterine arteries [135]. Studies have been published of Doppler study of flow through cardiac valves, beginning at 6 weeks [136, 137]. It should be noted that it is technically extremely difficult to obtain these tracings and, thus, *very* prolonged dwell times may be necessary. Some have described performing a measurement of the heart diameter, heart rate and inflow and outflow waveforms "after 5 weeks" [138]. No details are available on exposure levels. It should also be remembered that, at these early stages of pregnancy, fetuses measure 1–2 cm in length and are completely included in the beam, therefore generating "total body scanning" in B-mode, which is necessary to position the Doppler gate. Analysis of ductus venosus flow as well as characteristics of flow across the tricuspid valve have been shown to be helpful in screening for chromosomal anomalies in the first trimester of pregnancy, as an adjunct to measurement of the NT. Waveform analysis of the ductus venosus reduces the false-positive rate of the screening test [139, 140]. For example, in fetuses with increased NT but with normal karyotype, from 11 to 13 6/7 weeks, absent or reversed A-wave (atrial contraction) in the ductus venosus is associated with a threefold increase in the likelihood of a major cardiac defect, whereas normal ductal flow is associated with a 50 % reduction in the risk for such defects [141–143]. It is clear that Doppler is an important tool to study fetal health in early (and late) pregnancy [130] but appropriate precautions need to be taken to limit exposure in terms of clear indication, time and acoustic output [144].

Acoustic Output

Based on various sources, it appears that acoustic output (as expressed by various intensities) is much higher in Doppler than in B-mode: for instance, 34 mW/cm^2 for the I_{SPTA} in B-mode versus 1080 mW/cm^2 for spectral Doppler [35, 145]. Furthermore, as demonstrated in Table 1.2, the output has increased in all modes

Table 1.2 Changes over the years in I_{SPTA} (in mW/cm^2), mean (and range) in various ultrasound modalities[a]

Ultrasound modality	1991	1995	1998
B-mode	17 (0.3–177)	34 (0.3–991)	94 (4.2–600)
Pulsed Doppler	1140 (110–4520)	1659 (173–9080)	1420 (214–7500)
Color Doppler	148 (25–511)	344 (21–2050)	470 (27–2030)

[a]Adapted from [35]

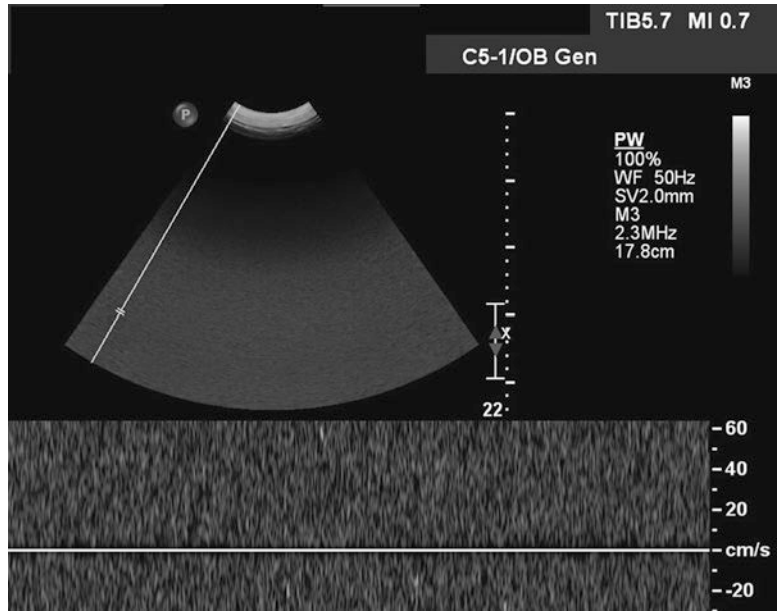

Fig. 1.3 Very high TI (5.7) may be obtained in Doppler mode (not an actual clinical examination). Note that this is a general obstetrics setting

over the years [35]. If one compares outputs (as expressed by TI and MI, a clinically easy-to-use but somewhat remote expression of output) between first, second and third trimesters, differences are not major [72] but higher TI values are obtained when switching to Doppler mode [74]. The increase in TI is, generally, small but with some new machines, TI's of up to 5–6 are displayed in Doppler mode (Fig. 1.3). Research has shown that excellent, diagnostic images can be obtained at low outputs, as defined by the TI values of 0.5 or even 0.1 [146]. This is illustrated in Fig. 1.4. Therefore, the switch-on default should be set up such that a low acoustic output power is initiated for each new patient, when starting an examination. Only if images are not satisfactory from a diagnostic standpoint, should the output be increased. Under pressure from Safety Committees of various societies, several ultrasound manufacturers have implemented this recommendation. Concerns about the fact that outputs are much higher in Doppler applications were expressed in three editorials [9, 147, 148]. In one of these, the authors raised the question whether research involving Doppler in the first trimester should even be considered for publication [147]. Based on these considerations, some recommend extreme caution when employing Doppler in the first trimester [149]. Furthermore, acoustic outputs, as published by the various ultrasound instruments manufacturers may not always be adequate [150] and an additional cause for concern is the increase in instruments outputs over the years [151]. Despite this, as detailed above, in recent years there has been a major recrudescence in the usage of Doppler in very early pregnancy. Unfortunately, one of the reason for this is the ignorance of many end-users of potential bioeffects, based on the "nothing has been shown" principle. Therefore, the risk is that this will become a routine standard, secondary to the push to utilize this modality by certain individuals, not necessarily knowledgeable of potential safety issues and that inexperienced end-users, wishing to imitate and adulate these "experts" will attempt to perform these exams for extremely extended period of time at pregnancy stages which are very susceptible to external insults (Christoph Brezinka, pers. comm.). Indeed, as mentioned earlier, a major issue is the lack of knowledge of ultrasound clinical users on output, bioeffects and safety, both in the USA [62] and abroad [61, 63, 64].

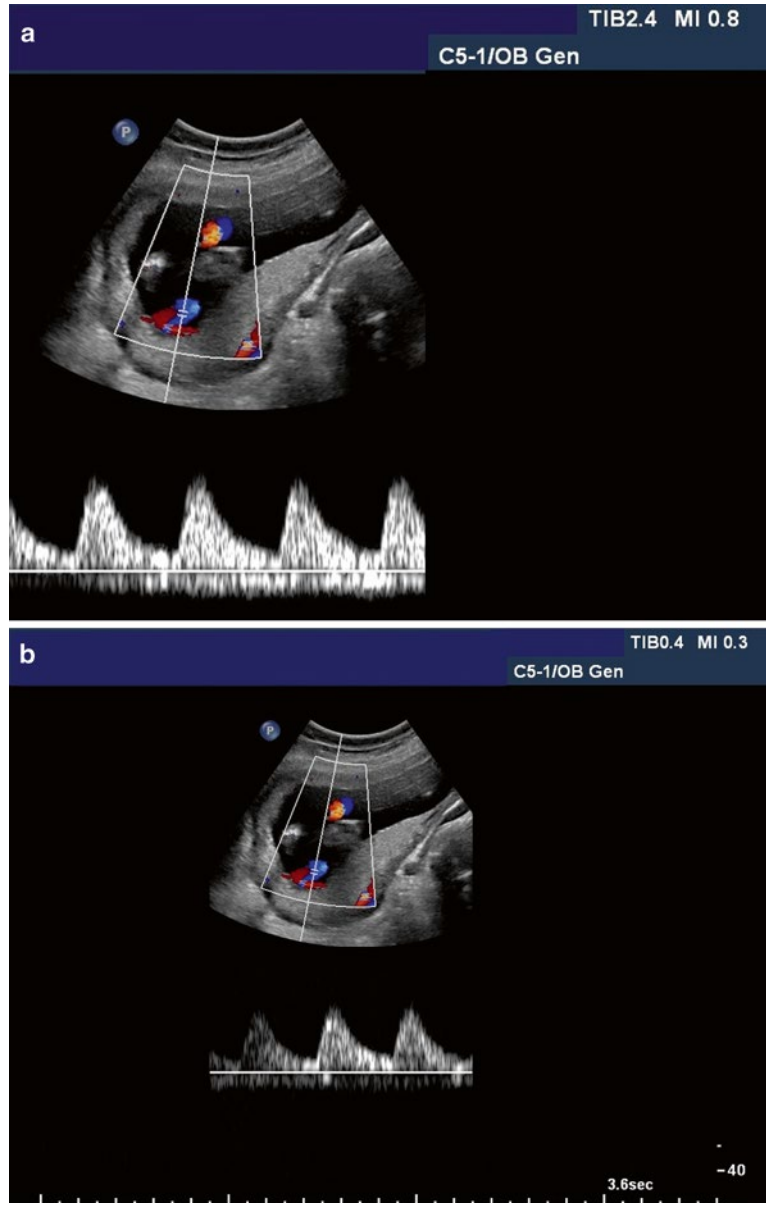

Fig. 1.4 Doppler velocimetry in the umbilical artery. (**a**) TI_B is 2.4. (**b**) The TI_B is 0.4 and the image is equally diagnostic

3D/4D Ultrasound

Three-dimensional (3D) as well as four-dimensional (4D) ultrasound are gaining recognition in obstetrics and gynecology. In prenatal diagnosis it adds to the detection of a wide range of anomalies, such as those involving the face, skeleton and extremities. The usefulness in early gestation is less obvious [152]. Characteristics are short acquisition time and post processing analysis, hence decreased exposure. As determined by TI and MI, acoustic output during 3D/4D exams does not seem excessive [75]. Figure 1.5 demonstrates low TI and MI during a 3D acquisition. The resulting reconstructed image is, obviously, a post-processing process. Sheiner et al. have shown that mean TIs during the 3D

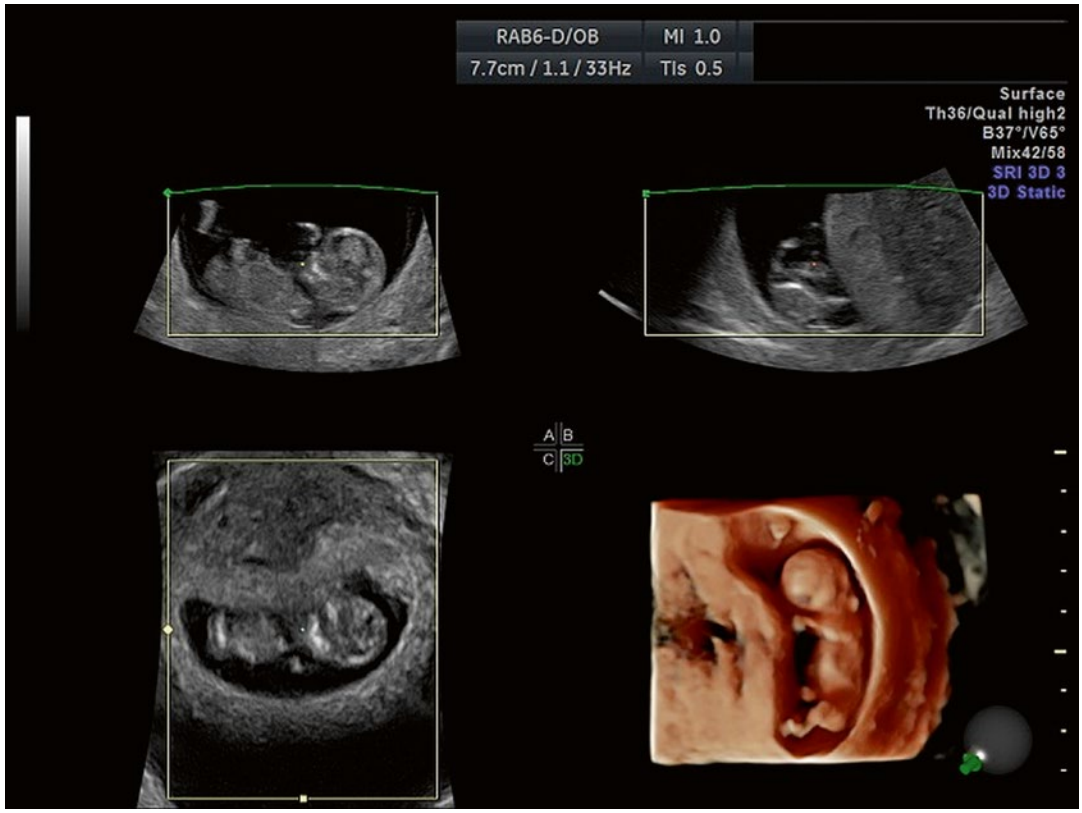

Fig. 1.5 Three-D acquisition with three orthogonal planes and reconstructed volume. The output power is determined by the acquisition plane (in general *plane A*), since the two other *planes* (*B*, *C*) and the reconstructed volume are computer-generated. In this acquisition, TI_S was 0.5

(0.27 ± 0.1) and 4D examinations (0.24 ± 0.1) were comparable to the TI during the B-mode scanning (0.28 ± 0.1; $P = 0.343$) [75]. The 3D volume acquisitions added 2.0 ± 1.8 min of actual ultrasound scanning time (i.e., including neither data processing and manipulation, nor 3D displays, which are all post-processing steps). The 4D ultrasound added 2.2 ± 1.2 min to the examination time. Amount of additional scanning time needed to choose an adequate scanning plane and to acquire a diagnostic 3D volume was not noted. Attractive views of the face, for instance, have led to its popularity among pregnant women who ask for non-medically indicated ultrasound ("keepsake ultrasound"). This is often performed in non-medical facilities, not for diagnostic purposes, in order to provide images for the family photo album. The issue was addressed long ago [153] but the practice has been opposed by various authors and professional, scientific organizations [154–164], although not by all [165] and with difference of opinions on whether practitioners involved in this activity should be sanctioned [166].

How to Limit Fetal Exposure and Safety Statements

The answer is simple: perform ultrasound only with a clear indication, keep exposure to a minimum power and time, compatible with an adequate diagnosis (application of the ALARA principle), watch the TI (and, to a lesser degree) the MI on-screen and do not perform examinations with new techniques "simply because you

can," if they have not been scientifically shown to afford diagnostic advantages [96, 127, 144, 167]. In general, begin your exam with a low power output and increase only if necessary [167, 168]. Some scientists have clearly stated that Doppler should be avoided in the first trimester. Several ultrasound organizations, however, have publishing statements and/or guidelines specific for first-trimester ultrasound, with a particular emphasis on the use of Doppler in early pregnancy. The following statement which summarizes the various guidelines is copied from the AIUM's website and is available to the public.

AIUM [169]: "The use of Doppler ultrasound during the first trimester is currently being promoted as a valuable diagnostic aid for screening for and diagnosis of some congenital abnormalities. The procedure requires considerable skill, and subjects the fetus to extended periods of relatively high ultrasound exposure levels. Due to the increased risk of harm, the use of spectral Doppler ultrasound with high TI in the first trimester should be viewed with great caution. Spectral Doppler should only be employed when there is a clear benefit/risk advantage and both TI and examination duration are kept low. Protocols that typically involve values of TI lower than 1.0 reflect minimal risk. In accordance with the WFUMB statement, we recommend that:

1. Pulsed Doppler (spectral, power, and color flow imaging) ultrasound should not be used routinely.
2. Pulsed Doppler ultrasound may be used for clinical indications such as to refine risks for trisomies.
3. When performing Doppler ultrasound, the displayed Thermal Index (TI) should be less than or equal to 1.0 and exposure time should be kept as short as possible (usually no longer than 5–10 min) and not exceed 60 min.
4. When using Doppler ultrasound for research, teaching, and training purposes, the displayed TI should be less than or equal to 1.0 and exposure time should be kept as short as possible (usually no longer than 5–10 min) and not exceed 60 min. Informed consent should be obtained.
5. In educational settings, discussion of first trimester pulsed or color Doppler should be accompanied by information on safety and bioeffects (e.g., TI, exposure times, and how to reduce the output power).
6. When scanning maternal uterine arteries in the first trimester, there are unlikely to be any fetal safety implications as long as the embryo/fetus lies outside the Doppler ultrasound beam.

It should be noted that paragraphs 1 through 6 are common to AIUM, The European Federation of Ultrasound in Medicine and Biology (EFSUMB), the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and the World Federation of Ultrasound in Medicine and Biology (WFUMB).

Summary

Ultrasound may, arguably, be the most important technology in the last 50 years in obstetrical clinical practice. Its advantages are numerous and its use has expanded from simply measuring a biparietal diameter to three-dimensional (3D) study of the brain or heart anatomy or "real-time 3D" (aka 4D) evaluation of fetal behavior. Not only is structural analysis possible but functional assessment of cardiac function is achievable with the use of Doppler applications. The fact this can be done is not a blanket permission to perform it with no control or limits, particularly in early pregnancy, a time when the fetus is very susceptible to external insults. No gross harmful bioeffects have been described in humans as a result of using DUS but indications to perform an examination should be clear and the lowest possible acoustic output power should be used, for the shortest possible time, yet compatible with accurate clinical diagnosis [18]. Clinical end-users should be educated in bioeffects and in ways to keep the fetus safe.

Teaching Points

- Biological effects have been demonstrated with the use of ultrasound in animals but not in humans.
- Epidemiology data are from before 1992, when acoustic outputs were increased several folds.
- The early fetal period is a time of increased susceptibility to external factors, such as hyperthermia, a recognized teratogen, with the central nervous system (CNS) being most at risk.
- Bioeffects of ultrasound may be secondary to two major mechanisms: thermal (indirect, resulting from conversion of acoustic energy into heat) and non-thermal (also known as mechanical, direct effects caused by bubble cavitation and other mechanical phenomena).
- The Output Display Standard (ODS) is designed to give the end-user an idea of exposure and includes the Thermal and Mechanical indices (TI and MI).
- To ensure safety of ultrasound in early pregnancy, a clear and valid indication for use should exist.
- New indications include screening for genetic disorders, ductus venosus and tricuspid Doppler and cardiac function analysis which have the potential for bioeffects, secondary to usage in early gestation, a time of increased susceptibility and/or increased acoustic power.
- To limit exposure and potential harmful effects, use ultrasound only when indicated, keep the exam as short as possible, at lowest possible output for diagnostic accuracy (ALARA principle) and keep TI and MI below 1.

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Ultrasound and Infertility

2

Sana N. Khan and Elizabeth E. Puscheck

Infertility is a growing problem in the USA and worldwide. In the developed world, approximately 12–40 % of the population reports infertility or subfertility, while one in every four couples in the developing world is affected by infertility [1–3]. In the USA, from 2006 to 2010, approximately 7.4 million women, aged 15–44, utilized some infertility service [4]. Typically, an infertility evaluation is performed after 1 year of unprotected intercourse, for women under the age of 35 and after 6 months, for women at or older than age 35. The traditional infertility evaluation included a history and physical exam, hysterosalpingogram (HSG), semen analysis, and laboratory evaluation (TSH, prolactin, early follicular FSH, LH, and estradiol level, and a mid-luteal progesterone level).

Over the last 30 years, ultrasound has transformed the practice of reproductive endocrinology and has become central to any infertility evaluation and treatment. In the late 1980s, the endovaginal or transvaginal sonography was developed, which utilized a higher frequency probe than transabdominal probes. This probe placed vaginally is in close proximity to pelvic organs, resulting in much improved resolution, based on the inverse relationship between the sound frequency of the probe with improved resolution and the shorter depth of penetration of sound waves. In other words, higher frequency probes (such as 6–9 MHz recommended for transvaginal probes) allow for better resolution of nearer objects (such as the uterus and ovaries), but have a shorter depth of penetration. In most cases, this is sufficient to evaluate the ovaries, often found in the posterior cul de sac [5, 6]. Infrequently, the ovaries are located high and outside of the pelvis; in which case, a transabdominal probe (typically 2–5 MHz) may be necessary to locate the ovaries, or to assess the large fibroid uterus. Based on the above foundations, the transvaginal probe ultrasounds have become the preferred modality to examine pelvic structures, over all other imaging modalities. Ultrasound does have limitations: ultrasound cannot transmit sound waves through very dense fibroids, and the position of the uterus in certain planes may also limit visualization. Furthermore, ultrasound examination may be limited by body habitus, such as in obese patients in transabdominal sonography; however a transvaginal approach may have less limitation in visualization.

Ultrasound is used regularly in the evaluation, monitoring, and treatment of the infertile couple. In the female patient, ultrasound is used for the initial workup, which includes a baseline

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ultrasound to evaluate the uterus, ovaries and general pelvic anatomy and an HSG or a saline infusion sonohysterogram (SIS)/sonosalpingogram (SSS) assessment of the uterine cavity and tubes for patency. This evaluation is usually performed in the beginning of the menstrual cycle (cycle day 1–3), when the endometrium is expected to be thin and the ovaries should be relatively quiescent, according to the Rotterdam criteria [5].

Baseline Evaluation

A systematic approach to ultrasound of the pelvis begins with a complete sweep through the pelvis from one side to the other side, visualizing the cervix, uterus, ovaries, adnexae, and cul-de-sac, to ensure that no part of the exam has been omitted. The exam commences during the placement of the endovaginal probe in the vagina, and the bladder is initially evaluated. The bladder is optimally empty during pelvic examination, but if not, the bladder should be inspected for any abnormalities and then ask the patient to empty her bladder.

Uterus

Initial evaluation of the uterus begins with identifying the cervix at the end of the vagina and just below the bladder. The cervix should be examined for any pathology or defects (i.e., Nabothian cysts). In pregnant women, we recommend measuring the cervical length from the external os to the internal os (the junction of the endometrium) (Fig. 2.1). The cervical orientation can be helpful in directing the examiner to the rest of the uterus and help identify its location and position.

The baseline evaluation of the uterine body traditionally includes several features, comprising the overall size in standard dimensions of the uterus (length, height, width), position, the consistency of the endometrium, as well as any defects of the uterus or other pathology. The uterus is typically measured in the mid-sagittal plane for the longitudinal length and the height, measured in the anterior–posterior (AP) diameter (Fig. 2.2a). The length extends from the end of the cervix (external cervical os) to the top of the fundus. The transverse measurement of the uterus

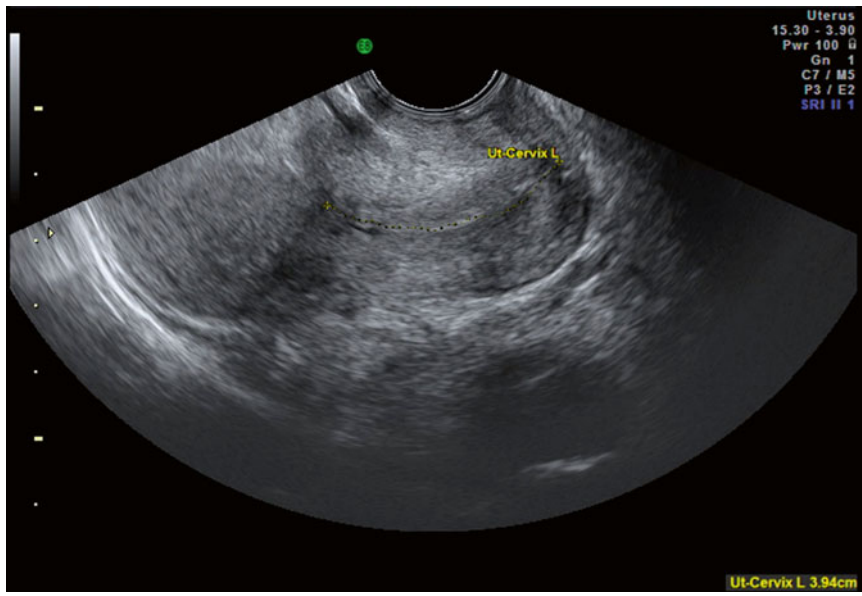

Fig. 2.1 Cervix measurement

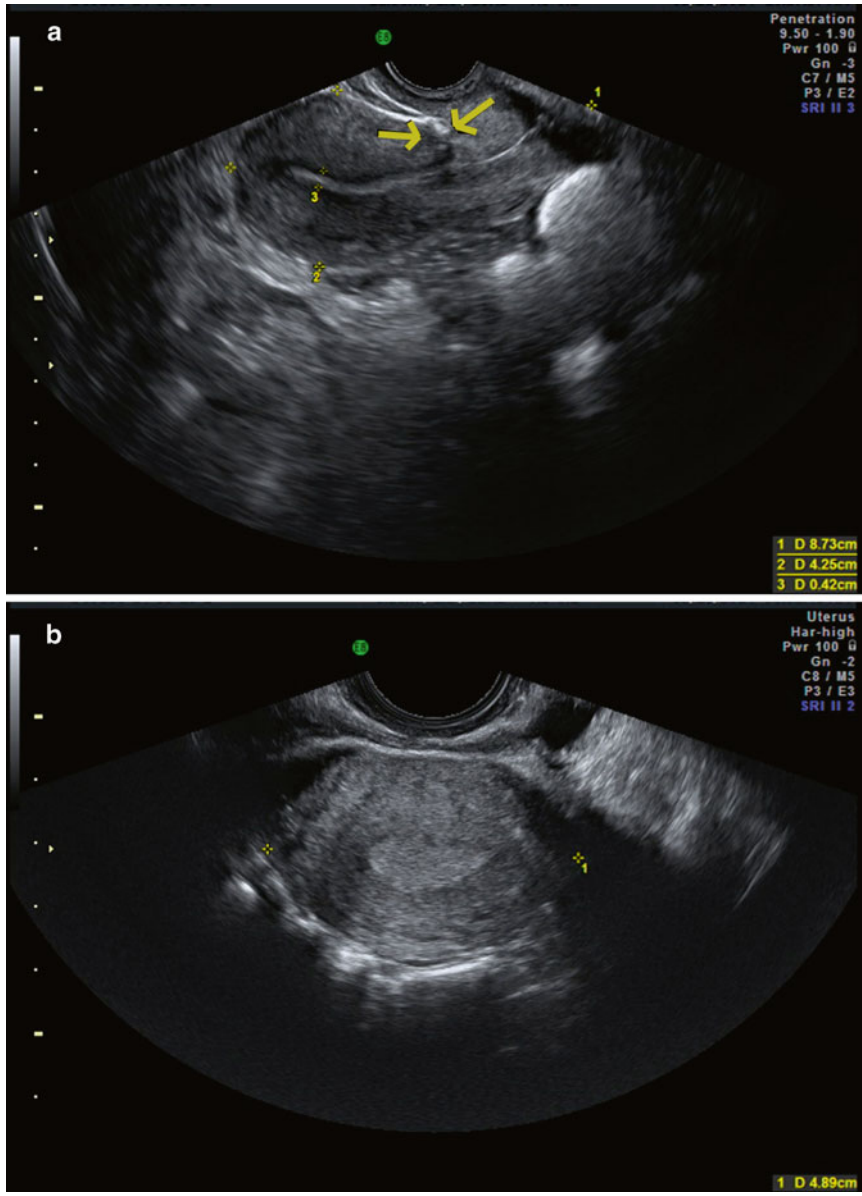

Fig. 2.2 Uterus measurements. (**a**) Longitudinal (*1*) and anterior-posterior (*2*) measurements for length and height. (**b**) Transverse view, *1* = width. The endometrium is thickened, consistent with the luteal phase. The arrows indicate the presence of a C-section scar

is also measured in the mid-corpus (see Fig. 2.2b). Additionally, the endovaginal ultrasound probe can be used as an extension of a pelvic examination to assess cornual tenderness, as well as a sliding organ sign, to show the movement of the ovaries in relation to the uterus, to establish fixed areas or adhesive disease [7]. Therefore, it is not only the images captured during the ultrasound, but much more information that can be gathered during the process of active sonography.

The size of the uterus corresponds well to the overall estrogenation of the body, with lower and normal/elevated estrogen values correlating with smaller and larger uterine size, respectively.

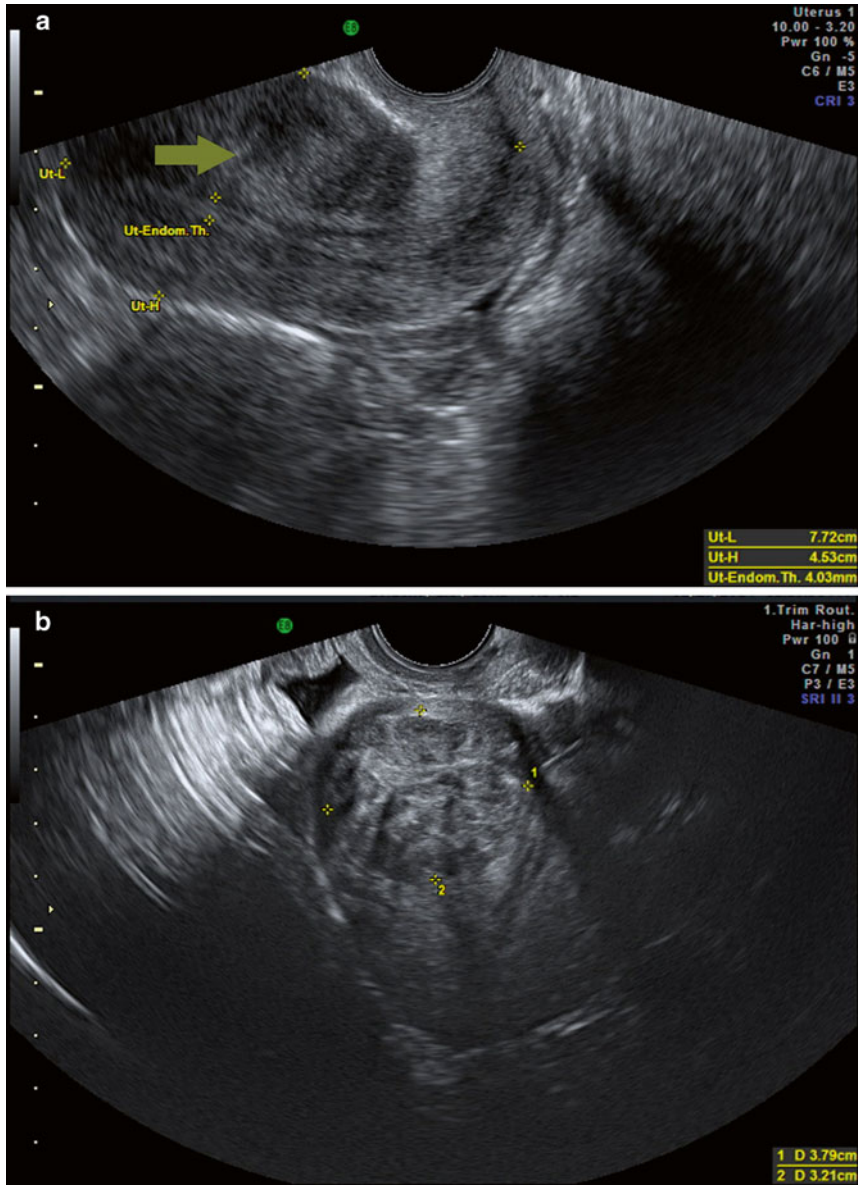

Fig. 2.3 Fibroids. (**a**) Intramural. (**b**) Subserosal

The assumption that smaller uteri may be associated with adverse pregnancy outcomes is erroneous; in fact, larger uteri were more highly associated with ectopic pregnancies in IVF/ICSI cycles [8]. The position of the uterus is also routinely recorded as a dynamic measurement. This information is important for procedures such as embryo transfer, which is subsequently discussed; furthermore, if the uterus is noted to remain motionless on serial exams, the concern is raised for adhesive disease or an entrapped uterus [9].

The uterine evaluation may reveal factors that contribute to infertility or result in early pregnancy loss. Common uterine abnormalities include polyps, fibroids, intrauterine adhesions, cesarean section scars, and congenital uterine anomalies. Submucosal fibroids (Fig. 2.3a) may affect early reproductive outcomes, by impairing

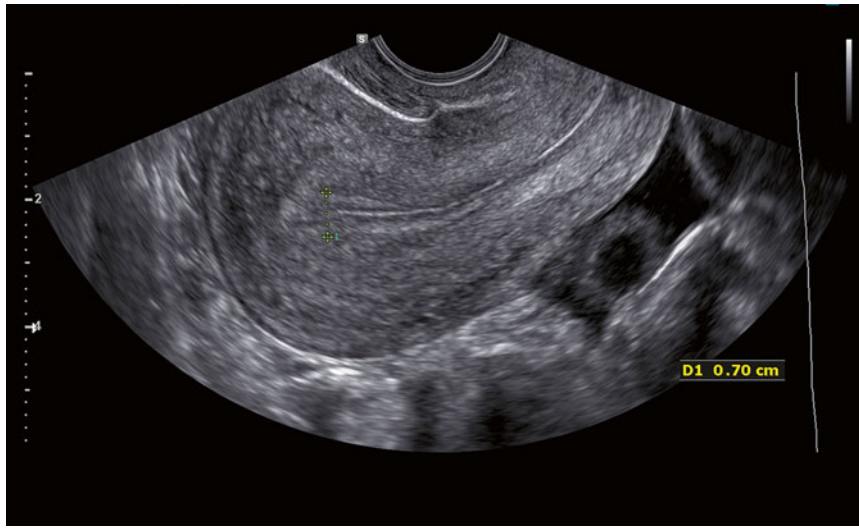

Fig. 2.4 Proliferative endometrium with trilaminar appearance

blood flow to the endometrium/myometrium, resulting in failed implantation and pregnancy loss. Surgical correction of these defects has been found to improve pregnancy outcomes. In contrast, intramural fibroids (see Fig. 2.3b) may also increase pregnancy loss, but surgical correction does not reduce the loss rate [10]. Some fibroids may grow large enough to impact the tubal ostia, making the passage of gametes into and out of the fallopian tube more difficult [11].

The endometrium is known to be a dynamic endocrine organ, which prepares itself and receives the developing embryo. Therefore, the endometrium is an important focus of the evaluation and treatment of the infertile patient. The overall thickness of the endometrium, when measured across the AP diameter, is correlated with the overall estrogenization of the pelvic organs. The endometrial lining is expected to be very thin during the initial part of the menstrual cycle, when estrogen levels are at a nadir, and is noted to increase around the time of ovulation and into the luteal phase, when the lining thickens in preparation of implantation (see Fig. 2.2b). Pathologies of the endometrium are known to affect reproductive outcomes, and are evaluated during the baseline examination. Intracavitary adhesions may be noted by an irregular or thin endometrium. Conversely, the presence of a thickened endometrial lining, on baseline ultrasound, may indicate a polyp or other defect is present within the endometrial cavity, which may need further evaluation to understand its impact on fertility. The thickness of the endometrium can be an indirect indicator of anovulation and possibly hyperplasia.

The ultrasound echo pattern of the endometrium is typically noted and followed during a treatment cycle. In the follicular phase, the endometrium grows in thickness and has a trilaminar appearance (Fig. 2.4). After ovulation, the endometrium becomes uniformly hyperechoic in this luteal phase portion of the menstrual cycle. These patterns have not correlated with pregnancy outcomes but this is often used as a part of the clinical assessment.

The presence of endometrial glands and stroma located within the myometrium is termed, adenomyosis. Adenomyosis is known to be clinically associated with dysmenorrhea, abnormal uterine bleeding and pelvic pain [12]. Adenomyosis is traditionally diagnosed histologically; however, several ultrasonographic features are thought to indicate the presence of adenomyosis (Fig. 2.5). These include cystic areas in the myometrium as well as increased vascularity along the periphery of the uterine body [13]. These findings have been described as "venetian blinds" secondary to the shadowing produced by these defects on

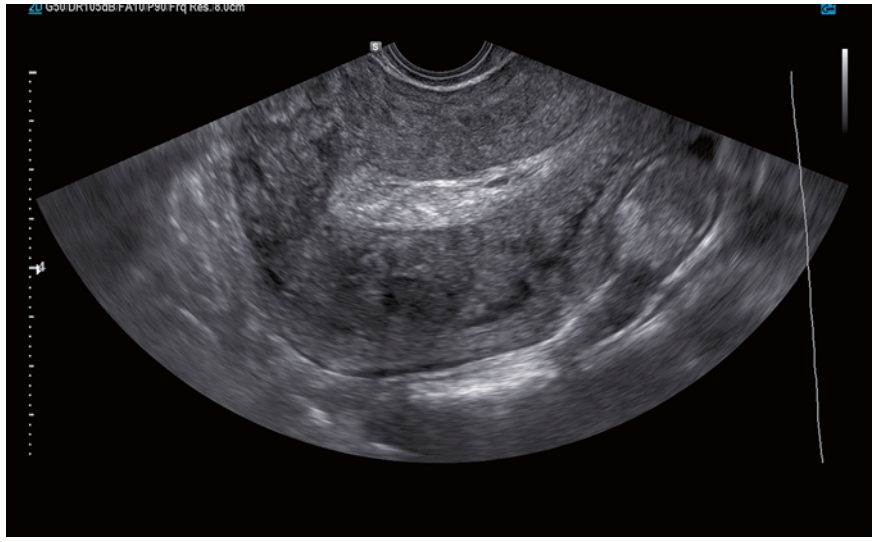

Fig. 2.5 Adenomyosis

structures further from the ultrasound probe [14]. In addition, one can demonstrate asymmetry of the anterior and posterior aspects (in relation to the endometrium) of the myometrium. New information suggests that the presence of adenomyosis decreases reproductive outcomes after infertility treatment such as in vitro fertilization (IVF). Therefore, some sources are recommending sonographic screening for adenomyosis in the subfertile population [15].

Ultrasound is used to rule out any suspicion of congenital abnormality of the uterus. Congenital uterine anomalies require 3D ultrasound or MRI to make the diagnosis, since the coronal surface of the uterus must be evaluated along with the endometrial cavity to distinguish between an arcuate uterus, a septate or subseptate uterus (Fig. 2.6), and a bicornuate uterus [16]. The luteal phase is the best time to perform a 3D ultrasound to assess for a congenital uterine anomaly since the endometrium will be thickened and hyperechoic and thus will act as its own contrast material [16].

Ovaries

As part of the baseline ultrasound evaluation, both ovaries are identified, measured in three dimensions, their position described (especially if located high out of the pelvis or posterior to the uterus) and the number of follicles (2–9 mm) in each ovary is counted (Fig. 2.7a, b). Any ovarian cysts or masses are described and further evaluation of these cysts/masses is performed with color or power Doppler.

The iliac vessels are used as a guide to find the ovaries and to determine the measurements. The length of the ovary is parallel to the length of the iliac vessel and the height is perpendicular to these measurements (see Fig. 2.7). Next, an orthogonal view of the same organ is performed, resulting in a transverse view of the iliac vessel (circle) with the ovary above it. The width of the ovary is measured in this transverse view. The ovarian volume can be determined using a modified ellipsoid formula or a 3D volume. The ovarian size can be diminished by hormonal contraceptives, smoking, menopause (including premature menopause), radiation, among other disorders. A large ovarian volume (>10 cm^3) is one of the measurements associated with a polycystic ovary appearance (Fig. 2.8) [6]. As expected, ovaries with cysts or masses will measure larger than normal.

In the infertility population like all reproductive age women, ultrasound is most likely to identify benign ovarian pathology when an ovarian mass is present. Physiologic or simple cysts may

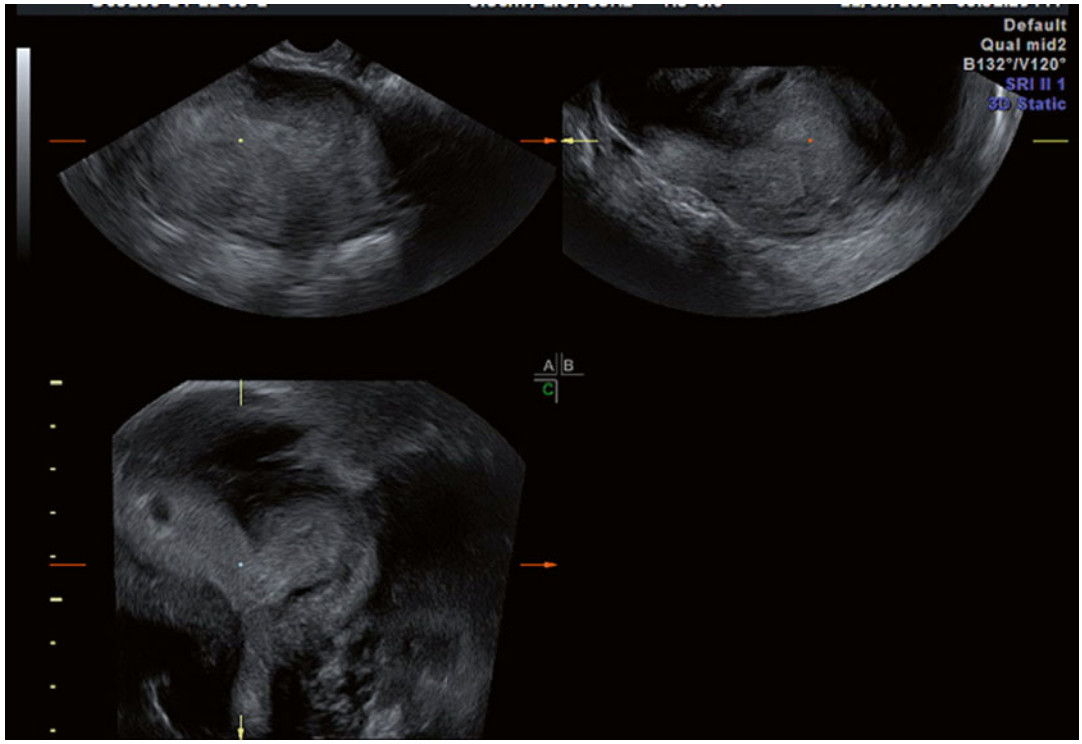

Fig. 2.6 Congenital uterine anomaly: subseptate uterus with a pregnancy in one horn

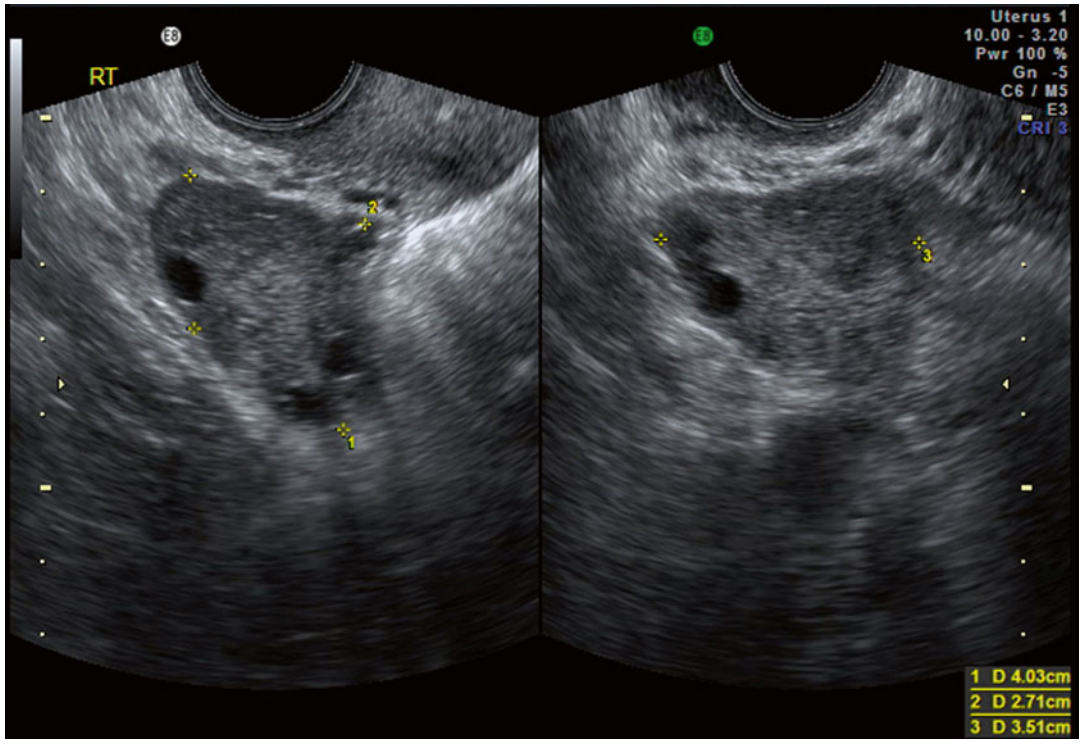

Fig. 2.7 Ovaries. (**a**) Longitudinal view in parallel with iliac vessels. *1* = length; *2* = height. (**b**) Transverse view with iliac vessel in transverse view (*circle*) with ovary width (*3*)

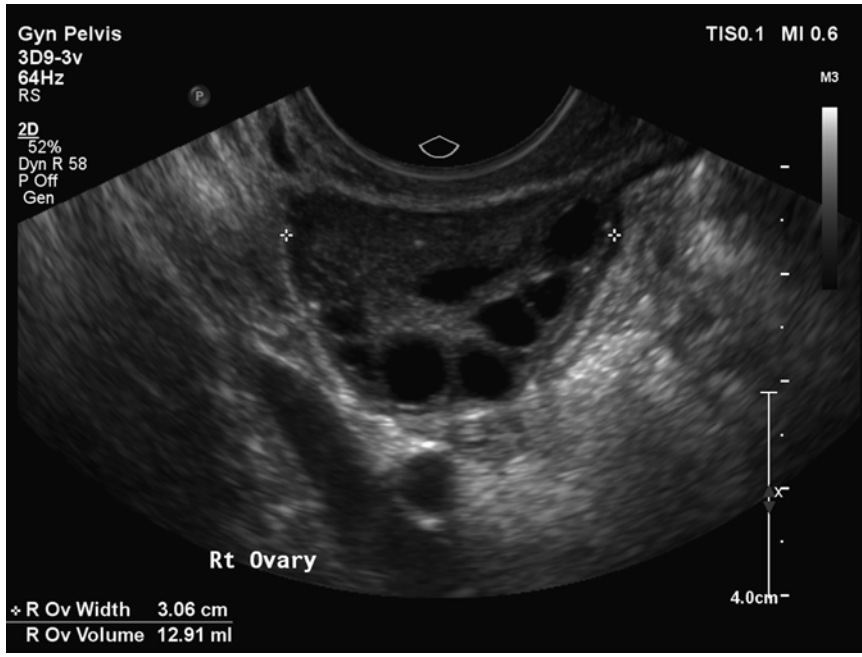

Fig. 2.8 A polycystic ovary (PCO). Several follicles are demonstrated in the organ. Periphery and the total volume of the ovary is increased above 10 cc

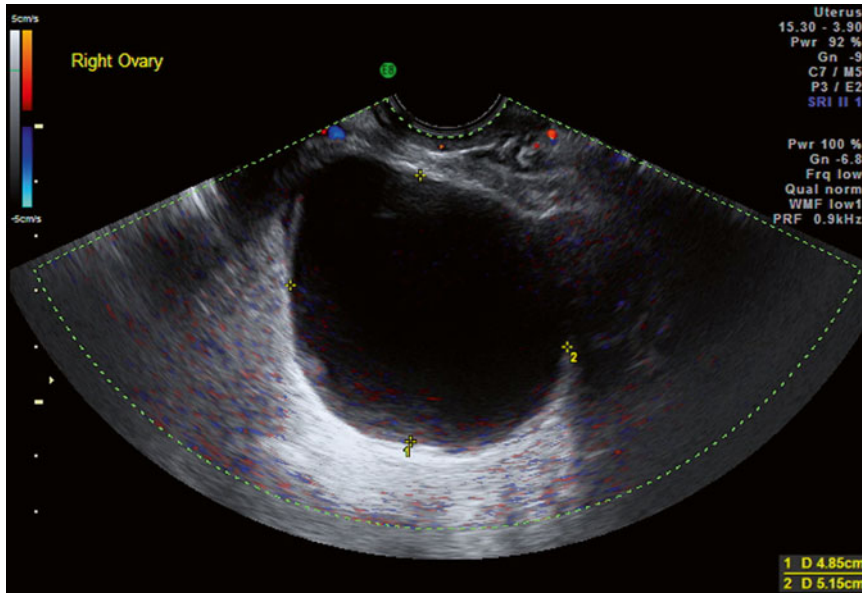

Fig. 2.9 Simple ovarian cyst. No Doppler flow within the cyst

be commonly visualized as follicular cysts, which are anechoic with no internal debris and usually round or potentially collapsed after ovulation (Fig. 2.9). These are thin-walled with posterior enhancement, and no internal color flow with Doppler ultrasound [17].

Other commonly visualized cysts include hemorrhagic corpus luteum cysts, endometrio-

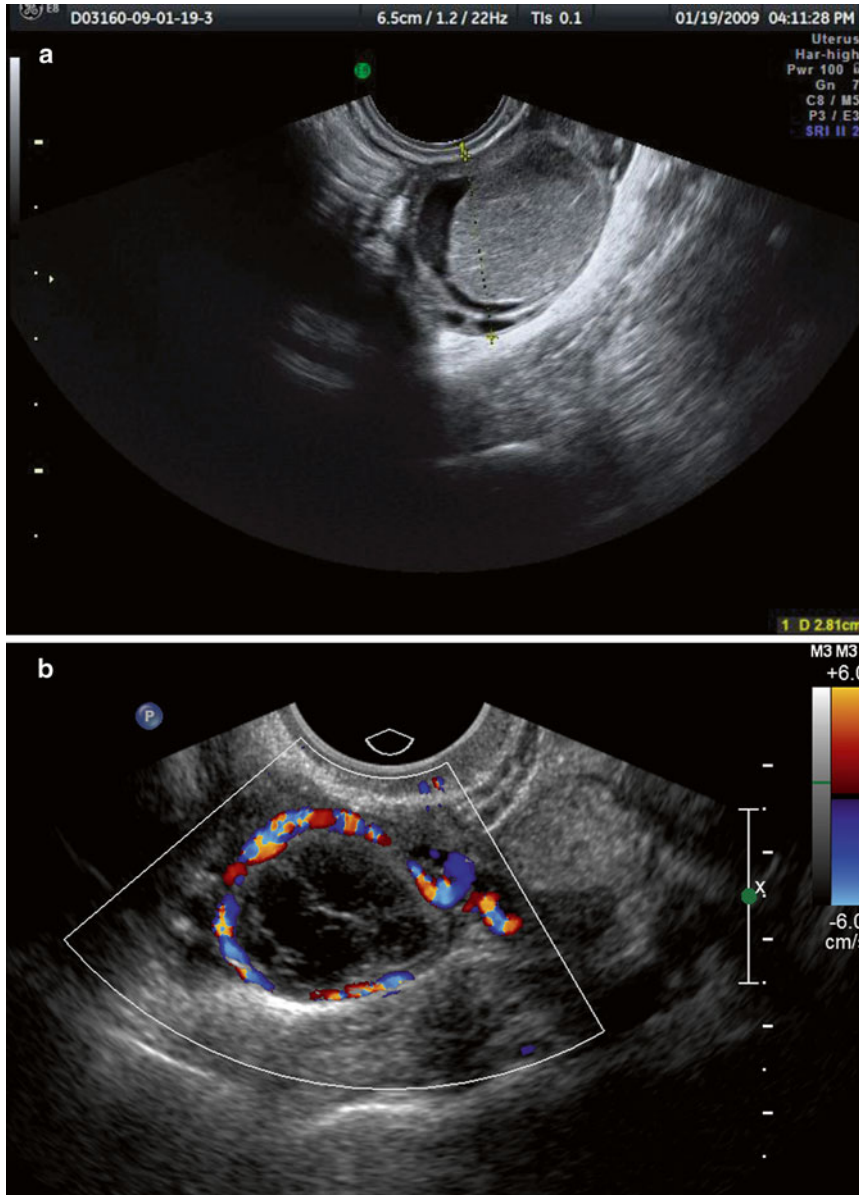

Fig. 2.10 (**a**) Hemorrhagic corpus luteum with solid and cystic components. (**b**) Hemorrhagic corpus luteum cysts. Internal echoes can be seen (organized clots, with reticular pattern due to fibrin strands). No internal flow is seen on color Doppler US but circumferential flow is clearly demonstrated ("ring of fire")

mas, and mature teratomas. Hemorrhagic corpus luteum cysts can have several appearances from an initial simple cyst when the blood is still liquid to more complex cystic masses, as the blood organizes into clots, which gives the appearance of a reticular pattern of internal echoes (a lacy appearance, generally due to fibrin strands) and/or, lastly, a combination appearance (cystic and solid), with solid-appearing area with concave margins, no internal flow on color Doppler ultrasound, and fluid (Fig. 2.10a). Usually the ovarian wall around the cyst has circumferential Doppler flow (see Fig. 2.10b) [17].

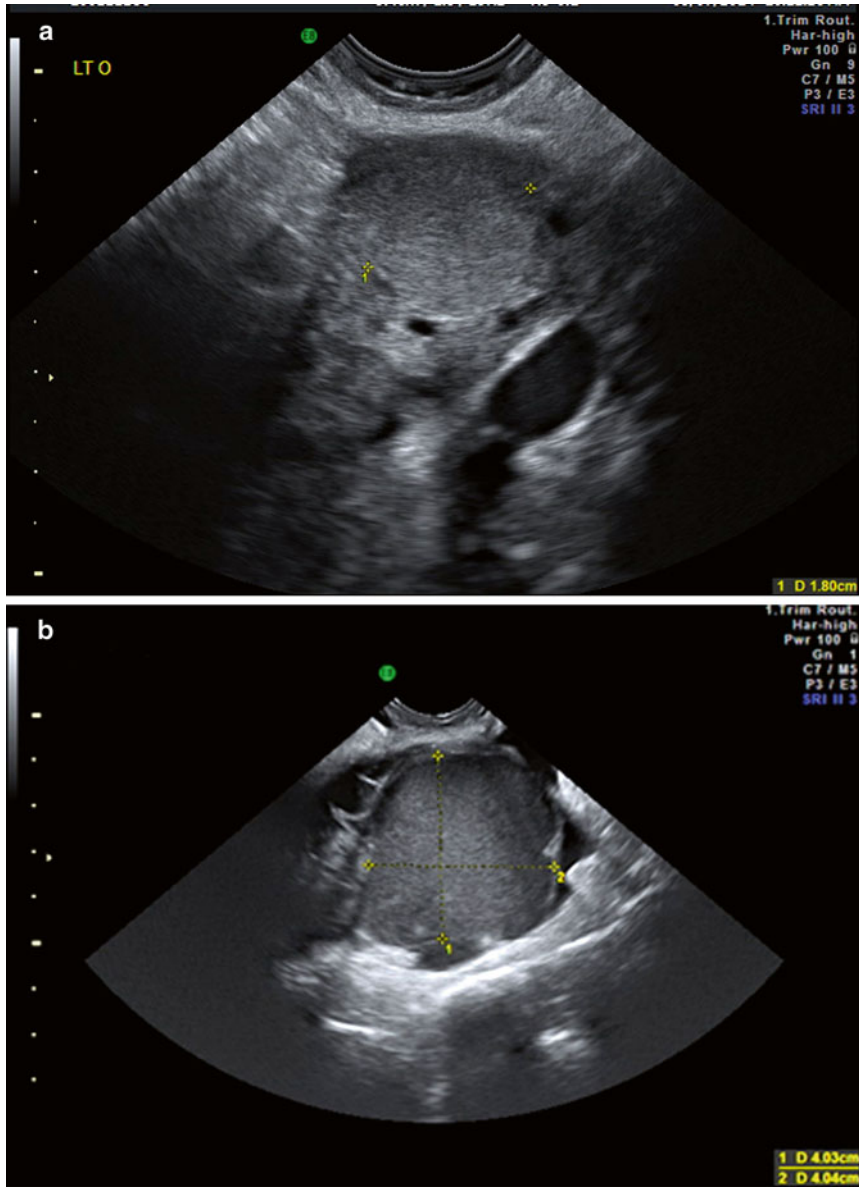

Fig. 2.11 (**a**) Endometrioma. (**b**) Endometrioma with atypical findings. The image shows the low-level echoes consistent with an endometrioma. The atypical features include the irregular borders and the hyperechoic small nodules

The typical endometriomas have internal homogeneous low-level echoes, sometimes described as a "ground glass" appearance, and have no internal color Doppler flow, wall nodules, or other neoplastic features. In such masses, the additional features of multilocularity and/or tiny echogenic wall foci may occur (Fig. 2.11a, b) [17]. Small endometriomas often do not need intervention and have not been found to affect reproductive outcomes [18–20].

"Dermoids" as they are commonly known are mature cystic teratomas of the ovary, consisting of sebaceous material, hair, and teeth. The ultrasound appearances of dermoids consist of focal or diffuse hyperechoic components, hyperechoic lines and dots, and area of acoustic shadowing, with no internal

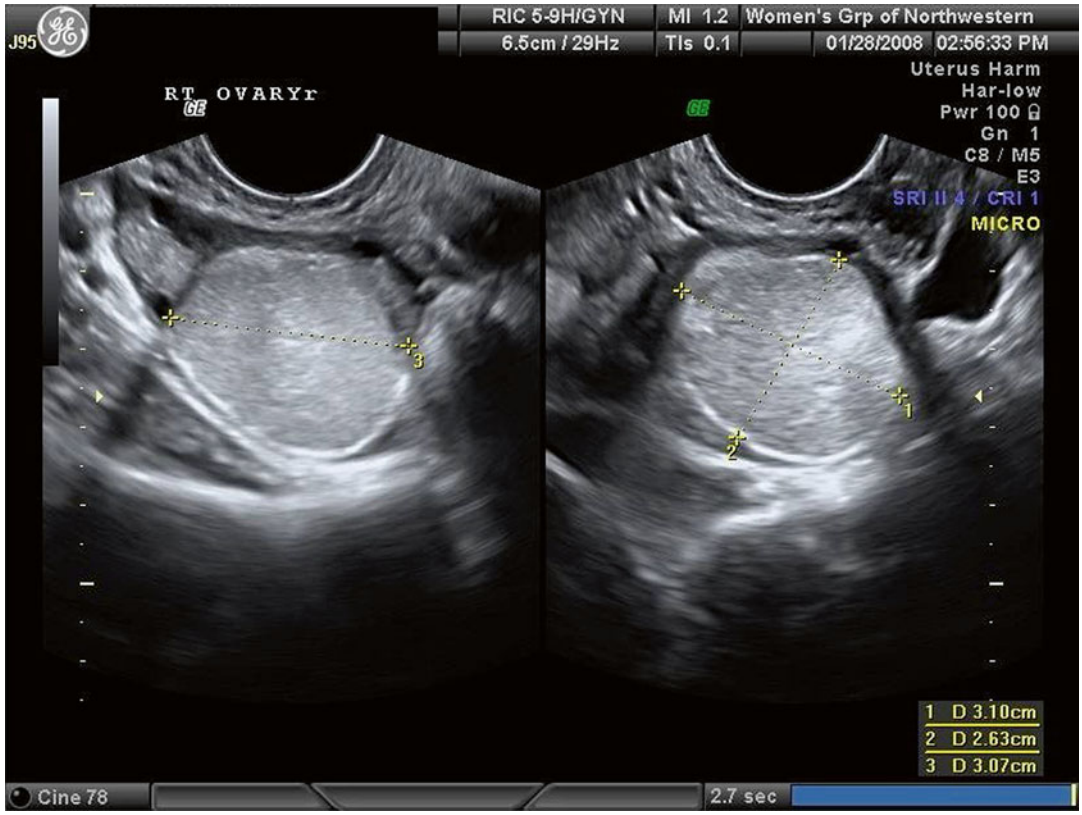

Fig. 2.12 Dermoid or mature teratoma. Courtesy of Leeber Cohen, MD

flow with color Doppler ultrasound (Fig. 2.12) [17]. Some have a nodule with shadowing called Rotkitansky's nodule. Color and/or power Doppler should be used to assess adnexal masses. No Doppler flow should be going into the dermoid or Rotkitansky's nodule. All abnormal findings need to be monitored with serial ultrasounds [17].

Other presentations to note include that of premature ovarian insufficiency patient, in whom the ovaries will be much smaller, consistent with menopausal patients and few or no antral follicles will be visualized. This finding helps establish the diagnosis, in a patient presenting with unexplained amenorrhea, and may help with fertility counseling.

Adnexa

Another critical component of the baseline ultrasound is to evaluate for any adnexal pathology. The most commonly encountered tubal findings are hydrosalpinx (Fig. 2.13a) and paratubal cysts or cysts of Morgagni. Both of these findings can be confused with a dominant follicle, instead of a diseased tube, and it is important that the provider performing the ultrasound clearly assesses the location of the pathology (in, versus adjacent to, the ovary) and view the pathology in three dimensions, to ensure that most information is gathered from the study (see Fig. 2.13b).

Miscellaneous

A variety of other findings are noted on the baseline ultrasound of the patient presenting with infertility. These may include free fluid around the ovaries or in the posterior cul-de-sac, as well as abnormalities in the bowel or surrounding structures. All abnormalities should be noted in the report.

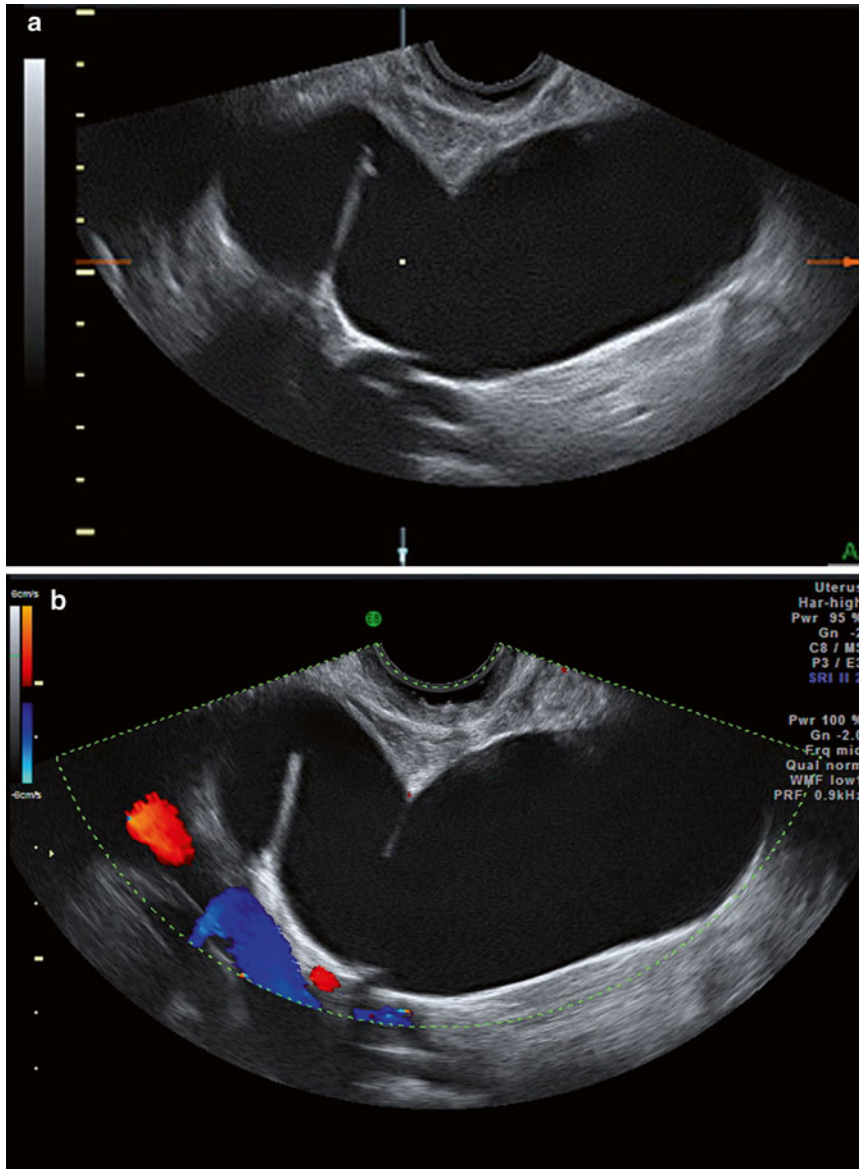

Fig. 2.13 Hydosalpinx. (**a**) Large hydrosalpinx. (**b**) Hydosalpinx en face can be confused with a blood vessel

Saline Infusion Sonohysterogram

During the initial workup of the infertile patient, in addition to the baseline ultrasound, one needs to perform an evaluation of the uterine cavity and an assessment of tubal patency. This information is critical in the decision of need and type of treatment offered to the patient.

The uterine cavity is best evaluated as soon as possible after the menses is completed and before ovulation (cycle days 6–12). This evaluation has traditionally been a radiographic procedure, called a hysterosalpingogram (HSG) in which contrast dye is injected through a cannula into the uterine cavity under fluoroscopic guidance and x-rays are taken. Ultrasound can be used with saline infusion to perform a similar procedure, called a saline infusion sonohysterogram (SIS). This SIS procedure is reported in several studies to be superior to the HSG in evaluating the uterine cavity [21]. Although similar information is

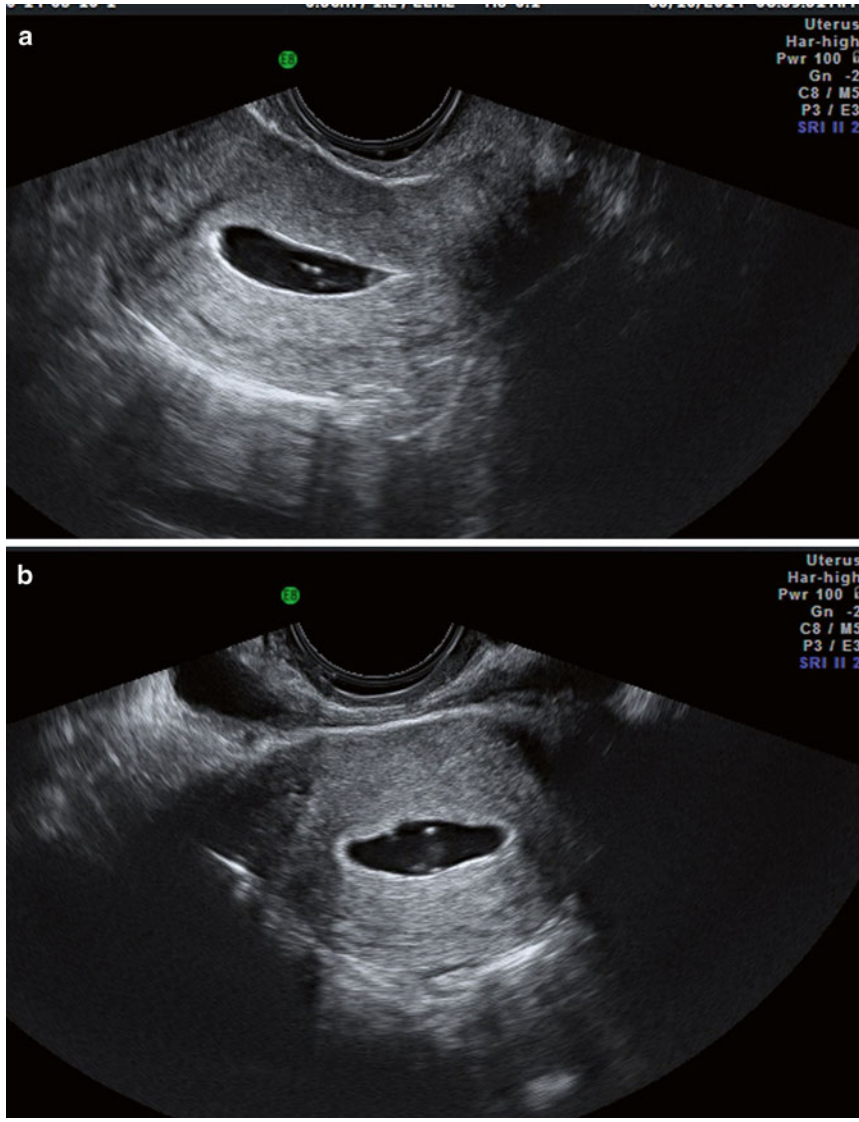

Fig. 2.14 Saline infusion sonohysterogram (SIS). (**a**) Sagittal view showing the longitudinal axis of the uterus with fluid, which appears *black* in the uterine cavity. No intrauterine filling defects. (**b**) Transverse view of the uterus with fluid in the uterine cavity at the mid-uterine level

gathered from an HSG, there is no radiation exposure during an SIS. Being able to perform and interpret the ultrasound exam in real time is a benefit of the SIS, and, unlike an HSG, this test may also reveal the diagnosis resulting in the abnormal filling defect (i.e., polyp, fibroid, adhesions). An SIS procedure is best performed in the early follicular phase after the cessation of menses, and after a baseline ultrasound has been performed.

During an SIS procedure, a patient is placed in lithotomy position, vagina and cervix are prepped, and then, typically, a small balloon or acorn catheter is placed into the cervix or endometrial cavity. If a balloon is used, this balloon is then inflated to create a seal, preventing liquid from escaping the uterine cavity through the cervix. Sterile saline is then injected and the uterine cavity is thoroughly examined in multiple planes, to detect any filling defects (Fig. 2.14a, b), such

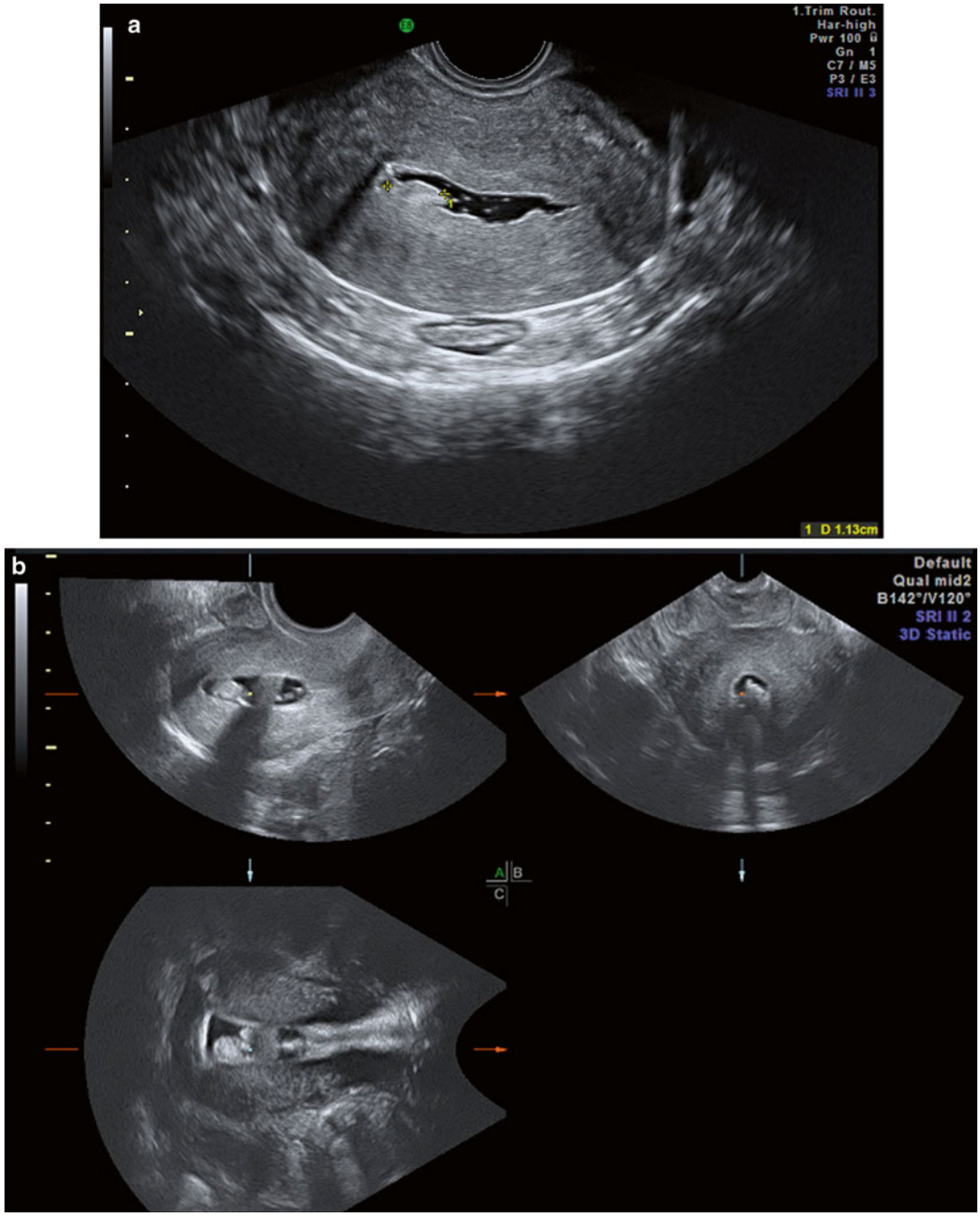

Fig. 2.15 (**a**) SIS of the uterus revealing a sessile polyp which measured at approximately 1 cm. (**b**) 3D SIS with polyp

as polyps (Fig. 2.15) or submucosal fibroid (Fig. 2.16) [22]. SIS used with color or power Doppler cannot only identify a filling defect (as noted by HSG), but also can identify the nature of the defect (i.e., polyp, fibroid, adhesion, etc.). Other pathology, which can be detected, includes endometrial adhesions, also known as Asherman syndrome (Fig. 2.17). In a population of subfertile women, SIS has been shown to be a highly sensitive tool and comparable to the gold standard tool,

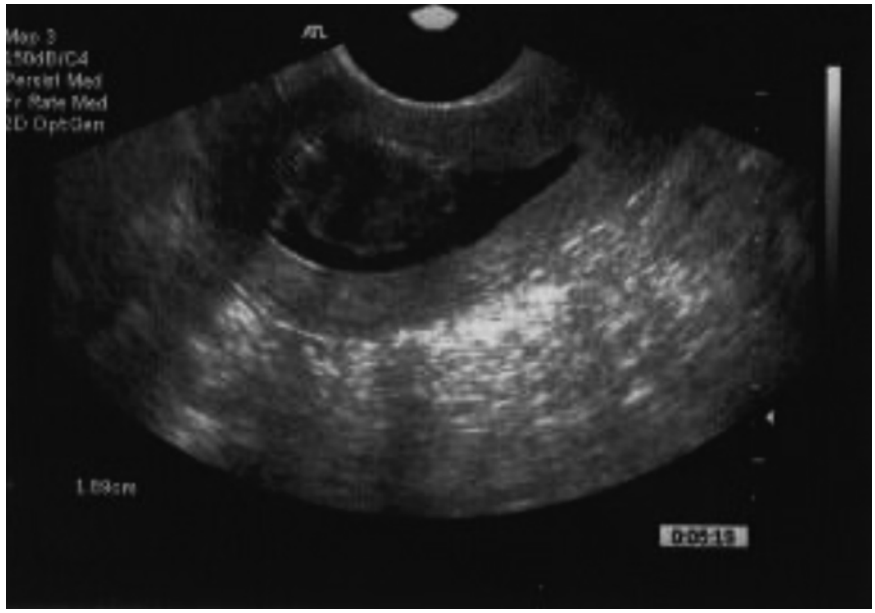

Fig. 2.16 SIS with submucosal fibroid

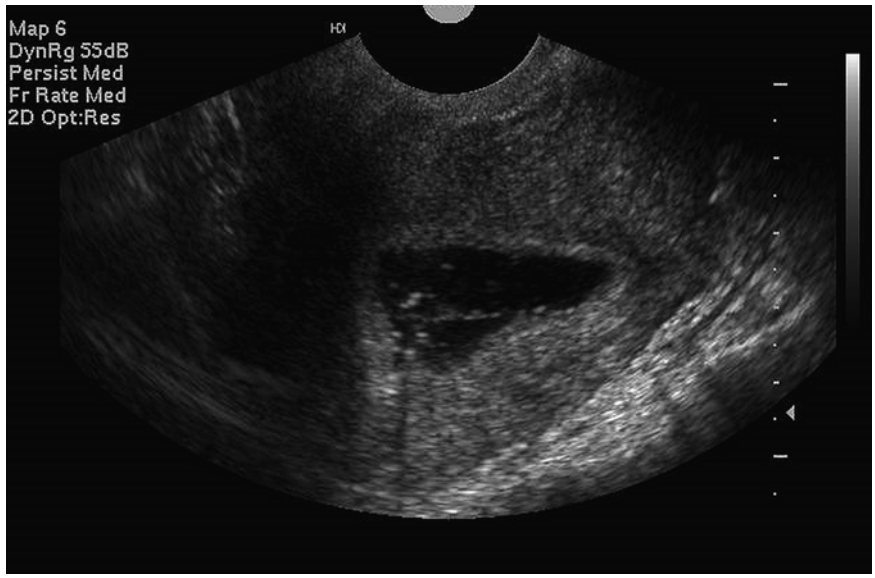

Fig. 2.17 SIS with intrauterine adhesions (Asherman syndrome)

hysteroscopy in the detection of intrauterine abnormalities [23]. The evaluation of the uterine cavity has traditionally been performed utilizing 2D ultrasonography, with the operator examining and sweeping through the cavity in sagittal and coronal planes, to evaluate the entire uterine cavity. Evidence, however, is now mounting regarding the use and possible superiority of 3D ultrasound for the assessment of the uterine cavity, which is discussed later in the chapter.

If a uterine anomaly is suspected, three-dimensional sonography (3D ultrasound) is often required to confirm the diagnosis. 3D ultrasound is also helpful in identifying the location of any intrauterine pathologies or the placement of an intrauterine device.

A more controversial topic is the use of ultrasound with agitated saline, in a saline sono*salpingogram* (SSS) to study tubal patency. This new term differentiates the assessment of the cavity (SIS) from the tubes (SSS). SSS may require a different skill levels to perform this examination.

Either preceding the evaluation of the uterine cavity or after, the fallopian tubes can be assessed. This is completed by the injection of agitated saline into the uterine cavity. Saline can be agitated either manually or by commercially available product. A new FDA-approved device, Femvue, can be used to detect tubal patency, through the mechanized installation of saline with bubbles into the cavity and fallopian tubes. Utilizing a transverse view of the uterine fundus near the cornua, agitated saline can be visualized with air bubbles traversing the proximal fallopian tubes. More specifically, the cornual portion of the uterus can be identifiable as a "lemon-appearing" transverse view of the uterus. It is often apparent to see a pencil thin line going from the endometrium into the proximal tube; however, if this is not observed, then the passage of the echogenic bubbles can be visualized traversing the cornua.

After both sides are examined, a thorough inspection of the pelvis ensues, either to detect a hydrosalpinx or to detect free fluid around one or both ovaries, or in the cul-de-sac. Of note, if agitated saline is not clearly visualized extruding through the uterine cornua, but free fluid was noted, at least unilateral tubal patency has been confirmed. Once the uterine cavity and fallopian tubes are assessed, the balloon is deflated and procedure terminated [22].

Besides the initial infertility workup, ultrasound is an integral part of infertility treatments: follicular monitoring, oocyte aspiration, and embryo transfers.

Follicular Monitoring Ultrasounds

Ultrasound is essential for the follicular monitoring of the infertile patient through their treatments. Low level, oral fertility treatments often do not require regular ultrasound monitoring. Midcycle sonographic confirmation of a dominant follicle, however, may be employed. Any treatments using gonadotropin injections for ovulation induction, or any form of in vitro fertilization (IVF) requires monitoring on a daily or every other day basis.

During the midcycle period, normally, the ovary produces a dominant follicle within cycle days 10–20. The goal of the infertility specialist is to time the intrauterine insemination at the time of ovulation, time ovulation trigger shot when the follicles are mature, or time the oocyte retrieval, so that the oocytes can be aspirated, prior to ovulation. This critical timing process depends on serial ultrasounds and the monitoring of the growth of ovarian follicles in the mid and late follicular phase. Most programs utilize 2D ultrasound. Newer software has been developed, however, to allow 3D image capture of the ovary and automated calculation of follicular volume through ovarian mapping, called SonoAVC [24, 25] (Fig. 2.18). Follicular monitoring revolves around the tenet that once recruited, a stimulated ovarian follicle is expected to grow by approximately 2 mm per day, as detected by ultrasound, until ovulation; therefore the frequency, timing, and reliable sonographic measurements from serial ultrasounds is extremely important. Ultrasound, additionally, offers a key advantage over hormonal monitoring alone, as many clinical situations introduce variability in the hormonal milieu, including perimenopausal patients and PCOS patients with high LH levels, which may obscure ovulation predictor kits [26].

Ultrasound in Assisted Reproductive Technology (ART) Procedures

Oocyte Retrieval

The invasive procedures associated with IVF include oocyte retrieval and embryo transfer procedures; both of which are routinely performed under ultrasound guidance.

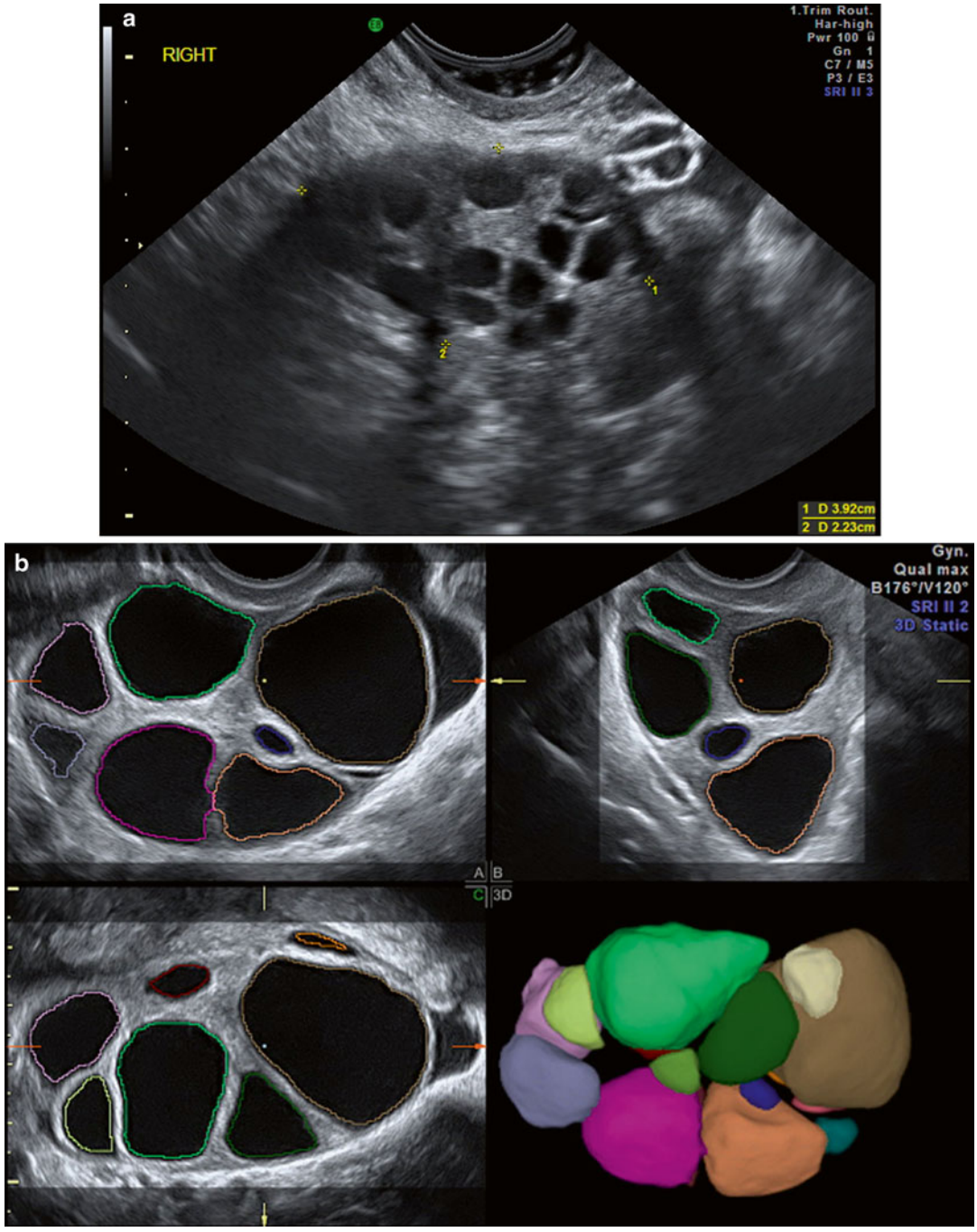

Fig. 2.18 (**a**) 2D view of a stimulated ovary with multiple follicles. (**b**) SonoAVC. Each follicle volume is automatically calculated and color coded corresponding to a table with measurements

The oocyte retrieval procedure relies on the tenet that stimulated ovaries will be larger and heavier and sink into the posterior cul-de-sac, where they can be easily visualized and reached with the use of an endovaginal probe. Historically, many other routes were attempted to retrieve

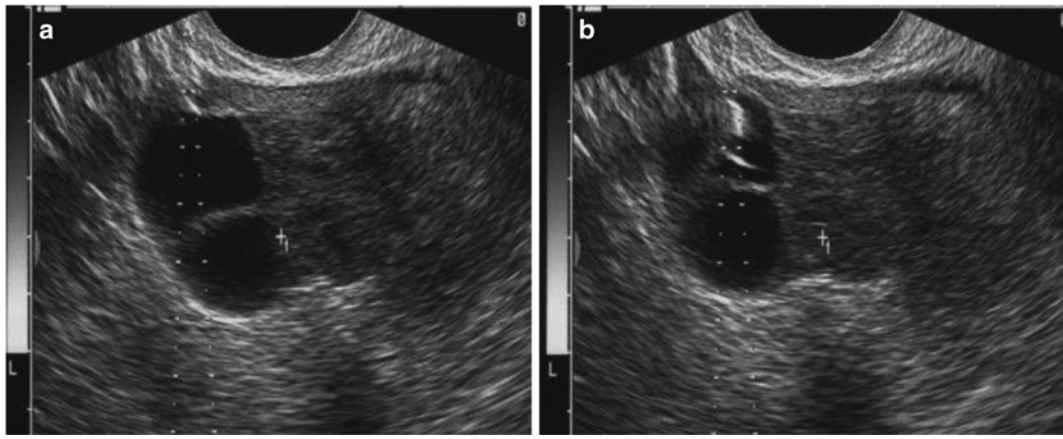

Fig. 2.19 Ultrasound image of oocyte retrieval. (**a**) Stimulated ovarian follicles with needle guide track. (**b**) Needle appears hyperechoic and is easily seen entering the mature follicle

oocytes, including laparoscopic, transurethral, and transvesical; the endovaginal approach, however, was found to be superior [27–29].

The endovaginal probe is fitted with a needle guide, which is projected onto the screen, so that the tract of the needle can be easily visualized and trajectory planned. The ultrasound probe can then be placed in the vagina near the ovary, needle inserted through the needle guide and into the ovary, where each follicle is serially aspirated (Fig. 2.19). This procedure obviously relies on the technical ultrasound expertise of the operator. Care must be taken since many vessels lie in the area near the ovaries, and these vessels may be confused with ovarian follicles, when seen on end [26, 30]. Some studies suggest that Doppler ultrasonography may hold the promise of increased safety during the procedure [31].

Finally, multiple studies have demonstrated that for patients in whom the ovaries are located abnormally high and out of the pelvis, these oocytes can be retrieved abdominally using the endovaginal probe for visualization [32, 33].

Embryo Transfer

Embryo transfer was originally performed without ultrasound guidance. Multiple studies, however, demonstrated improved outcomes when ultrasound was systematically used to ensure that embryos were being placed in the uterus and not in false tracts [34–36]. Since that time, the use of ultrasound guidance for embryo transfer has become routine. It is likely that the difference in pregnancy rates was secondary to those cases in which cervical abnormalities or uterine malposition was present, which increased the risk of non-endometrial embryo placement [37]. Thus, the importance of a skilled transabdominal sonographer is established in cases of difficult anatomy, to ensure that embryos can be placed in the uterine cavity additionally with minimal pain, bleeding or discomfort, all of which have been associated with uterine activity and lower pregnancy rates (Fig. 2.20a, b) [38].

In the near future, we anticipate that embryo transfer will be performed with real-time 3D ultrasound (see Fig. 2.20c) (4D ultrasound). Utilization of real-time 3D ultrasound may allow for more definite and accurate placement of the embryo transfer catheter, compared to 2D ultrasound, thus potentially improving embryo transfer technique [39, 40]. Of debatable significance is the three-dimensional volume estimation of the endometrial cavity as a marker of endometrial receptivity [41, 42].

Some studies suggest that 3D ultrasound can play a more important role in all elements of the evaluation and management of the infertility population [43, 44].

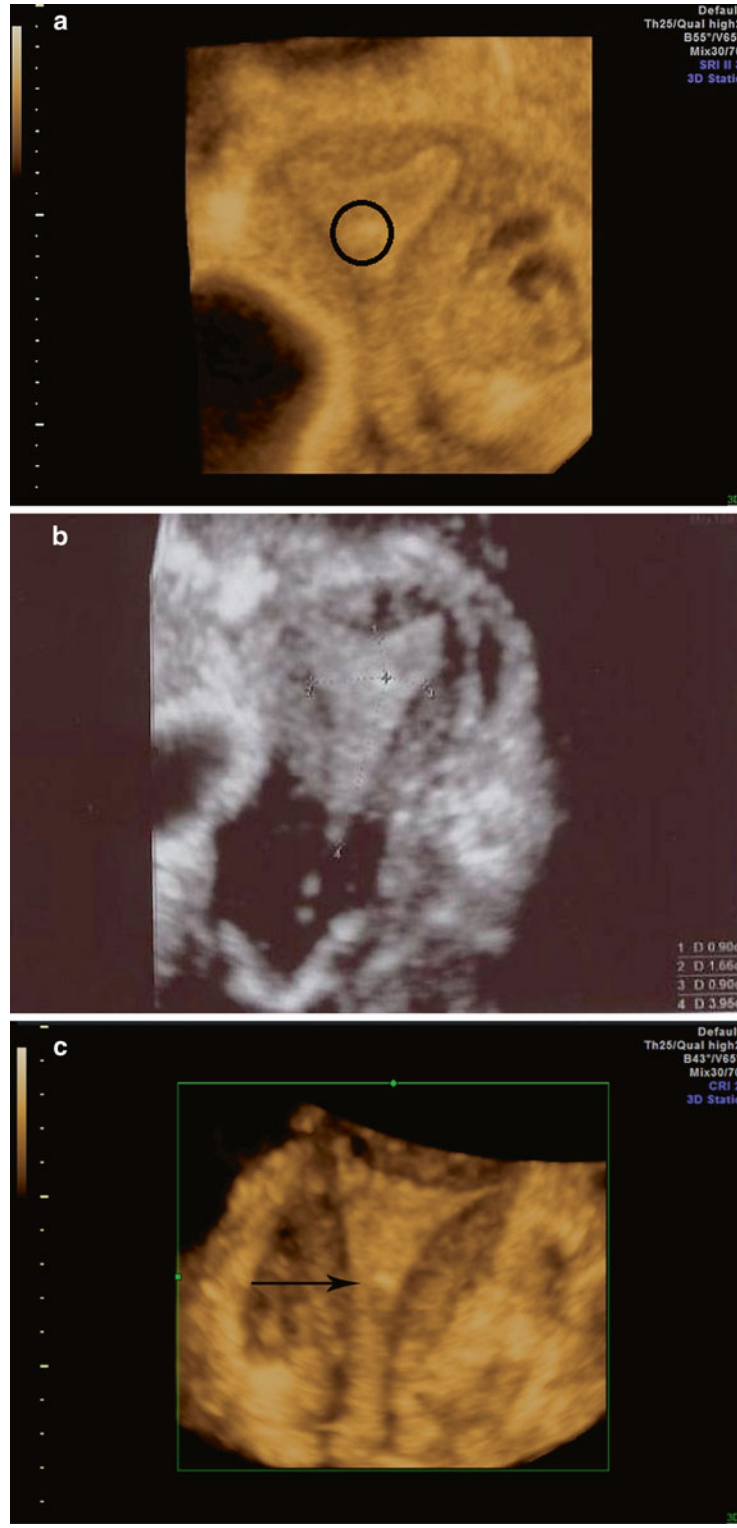

Fig. 2.20 (**a**) Abdominal ultrasound-guided embryo transfer with white spot correlating the air bubble that often accompanies the embryo and fluid at time of transfer. (**b**) Transvaginal outer catheter at the inner os and measurements to the top of the uterus and anticipated placement. (**c**) 3D rendered view showing *white spot* (*arrow*) corresponding to an air bubble that was released at the time of the embryo transfer

Miscellaneous

It must also be mentioned that the ultrasound forms a mainstay for the evaluation and monitoring of complications from fertility treatments, mainly ovarian hyperstimulation syndrome (OHSS). OHSS is a hormonally mediated vascular permeability disorder (related to VEGF and β-hCG), which is caused by controlled ovarian stimulation fertility treatments [45]. The clinical features of the disorder include potentially massive third spacing of fluid in the peritoneal, pleural, and even the pericardial cavities. Abdominal, pelvic, and even thoracic sonography are used to assess the amount of fluid in the peritoneal and pleural cavities, as well as to follow the size of the ovaries, which tend to be grossly enlarged despite oocyte retrieval (Fig. 2.21) [45, 46]. On occasion, drainage procedures are necessary, which are in general performed under ultrasound guidance as a paracentesis or culdocentesis [46].

Three-Dimensional Ultrasonography

There are many emerging applications of 3D ultrasound, including the evaluation of the uterine cavity, study of congenital uterine anomalies, follicular volume calculation programs and for optimal embryo transfer location. A recent study found that 3D SIS correlated better with hysteroscopy, which is known to be the gold standard [47]. 3D SIS performed better than traditional 2D ultrasound for the detection of intrauterine abnormalities; however, further, larger-scale research endeavors are needed to confirm these findings [47]. Additionally, the use of 3D ultrasound shows extreme utility for the diagnosis of congenital Müllerian anomalies. Recent research suggests that 3D ultrasound is very accurate at diagnosing abnormalities, which were correlated with endoscopic findings [48–51]. Furthermore, the agreement between 3D ultrasound and MRI findings was very high, indicating that 3D ultrasound may replace MRI for certain studies (such as diagnosis of congenital uterine anomalies or intrauterine device [IUD] localization), decreasing the cost and risk of radioactive contrast exposure [52].

Pregnancy and Recurrent Pregnancy Loss

Pregnancy determination is typically done about 12 days after the embryo transfer. When there is a positive pregnancy test, most infertility specialists

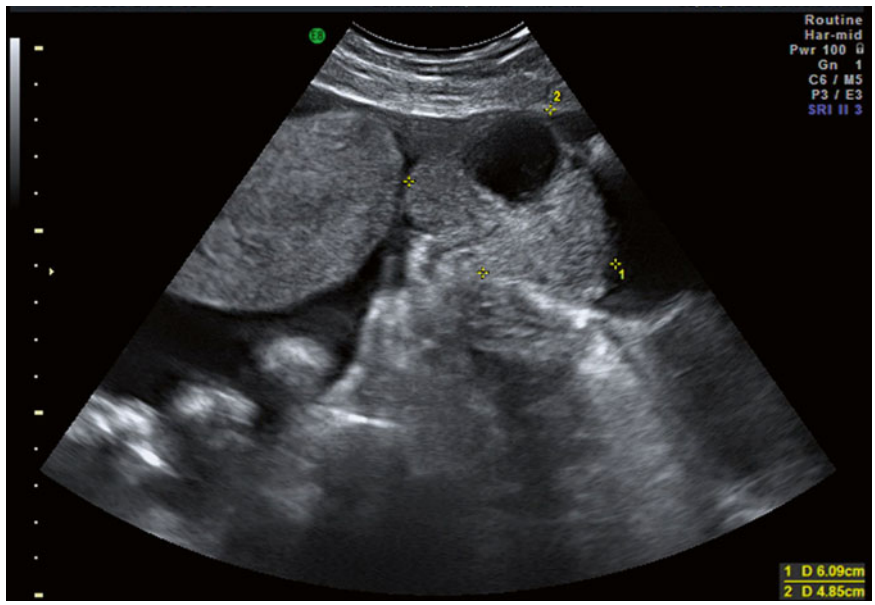

Fig. 2.21 Ovarian hyperstimulation syndrome. The abdominal cavity has a large amount of fluid with the uterus and ovaries floating within the ascites

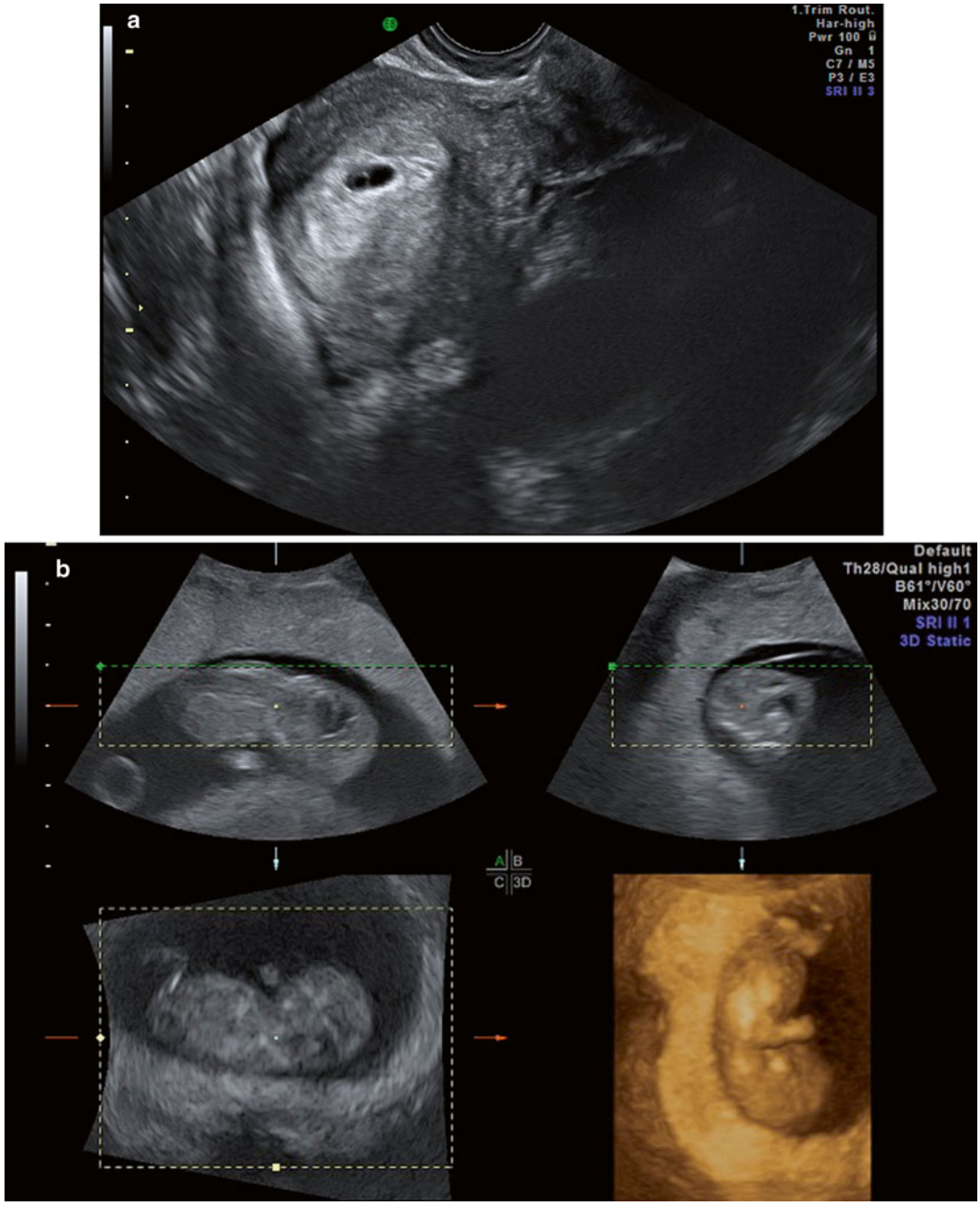

Fig. 2.22 (**a**) Early pregnancy with yolk sac. (**b**) 3D rendering of early pregnancy

will perform a second hCG level about 2 days later. If there is an appropriate rise, an ultrasound is typically scheduled at about 5.5–6.5 weeks, to confirm an intrauterine pregnancy (Fig. 2.22a, b). According to the American Congress of Obstetrics and Gynecology (ACOG), the estimated due date (EDD) should be determined based on the embryo transfer. If a day 3 embryo transfer is performed, the EDD is 263 days later [53]. If a day 5 embryo transfer is performed, the EDD is 261 days later. This is the most accurate dating available. Ultrasound should not re-date these pregnancies.

Other chapters discuss early pregnancy findings. Our patients tend to be very anxious, therefore a CPT code (V23.0) exists for "pregnancy with a history of infertility," which allows for more than the usual ultrasounds, to allay anxiety. The literature from recurrent pregnancy loss shows that "tender loving care" can improve pregnancy outcomes and these early ultrasounds are certainly reassuring. There are new terms and criteria regarding pregnancy loss and the determination of nonviable pregnancies [54, 55]. Infertility patients have about a 40 % incidence of threatened abortion presenting with vaginal bleeding. So these patients may present to the physician's office or the emergency room. It is critical that the pregnancy is not terminated inappropriately, since these patients have worked so hard to conceive. Doubilet et al. recommends waiting until the crown-rump length is 7 mm or more without fetal heart motion prior to declaring it nonviable. Our patients are eager to see the gestational sac, the yolk sac and most importantly the fetal heart motion in the uterus! When the fetal heartbeat is demonstrated, the likelihood of miscarriage is reduced significantly and, typically, the patient is referred back to the obstetrician for routine pregnancy care.

Recurrent pregnancy loss is also relegated to the REI for evaluation and treatment. Spontaneous miscarriage in the general population occurs in about 15–25 % of pregnancies and increases with age, approaching 50 % for women over 40 years old. Recurrent pregnancy loss is defined as two or more losses. Fewer than 5 % of women will have two consecutive pregnancy losses and less than 1 % of women will have three or more. The American Society of Reproductive Medicine (ASRM) produced a committee opinion, reviewing the evidence, and recommends the following workup: genetic evaluation of the parents and products of conception (karyotypic abnormalities are the most common cause, 60 %), anatomic evaluation of the uterus (SIS or HSG), endocrine evaluation for thyroid and prolactin abnormalities, anti-phospholipid evaluation (lupus anticoagulant, anticardiolipin antibody, anti-beta 2 glycoprotein 1), and psychological counseling [56]. One study referenced in this ASRM document reported significant improvement with tender loving care (TLC) in the form of: psychological support, weekly ultrasounds, and avoidance of heavy work, travel, and sexual activity, as compared with the controls, which led to a pregnancy rate at 85 % for the intervention group and 36 % for the control group [57]. ASRM cautions regarding the interpretation, since the groups were not randomized, but determined based on nearness of the subjects' residence. In couples completing an RPL evaluation, approximately 50 % will have no identifiable etiology for their miscarriages which are, thus, unexplained. It is important to emphasize that those with an unexplained etiology for recurrent pregnancy loss still have a 50–60 % chance of a future successful pregnancy.

Teaching Points

- Ultrasound is a critical part of the infertility evaluation and treatment.
- Traditional 2D ultrasound is used for the baseline evaluation of the uterus to evaluate uterine dimensions (3D if a uterine anomaly is suspected), ovarian dimensions and volume, ovarian antral follicle count (AFC), and any pelvic pathology.
- Saline infusion sonohysterography (SIS) is an important tool for the evaluation of the endometrial cavity and is comparable to hysteroscopy for the detection and diagnosis of intrauterine abnormalities when used with 3D ultrasound.
- Saline sonosalpingography (SSS) can be used to assess tubal patency by ultrasound using an agitated saline approach.
- Three-dimensional sonography is a required modality to diagnose congenital uterine anomalies or Intrauterine device placements (or misplacements). It is also used in infertility specifically for better assessment of the endometrial cavity and localization of intrauterine pathologies during SIS.
- Either 2D or 3D ultrasound is used for the monitoring of controlled ovarian stimulation to assess follicular growth and endometrial thickness.
- Transvaginal sonography is a critical component for Assisted Reproductive Technologies (i.e., oocyte retrieval and embryo transfer).

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3 Maternal Comorbidities and First-Trimester Ultrasound Examination

Elena Bronshtein and Karoline S. Puder

Introduction

Ultrasonography is one of the most important and useful diagnostic tools in obstetrics. It is a noninvasive, portable, quick, and safe technology. Ultrasound performed in the first trimester confirms an intrauterine pregnancy, establishes accurate dates, and is crucial in diagnosing early pregnancy failure and ectopic pregnancy. It is commonly used for risk assessment for aneuploidy, through measurement of nuchal translucency and identification of the presence or absence of the nasal bone. Moreover, ultrasound for fetal assessment of early pregnancy reduces the failure to detect multiple pregnancies by 24 weeks of gestation and is also associated with a reduction in induction of labor for post-term pregnancy [1]. Standard indications for first-trimester ultrasound are shown in Table 3.1. These are addressed in detail in various chapters of this book. Several maternal conditions are known to be associated with an increased risk of fetal anomalies and may justify early or more detailed fetal anatomy survey.

Recently, several studies encouraged the early diagnosis of major anomalies after demonstrating the association of increased fetal nuchal translucency (NT) and structural defects [2–4]. The development of high-frequency and high-resolution transvaginal ultrasound transducers, along with substantial improvement of the technology, has resulted in the visualization of fetal anatomic structures in greater detail earlier in gestation [5–16]. This helps to shift the prenatal diagnosis from the standard second-trimester anatomy scan into the first trimester, and also gives the opportunity for pregnancy termination in appropriate cases of anomalies identified earlier in gestation. On the other hand, the absence of major fetal structural malformations in the first trimester can reassure patients and reduce anxiety.

While there are some anomalies that will not be evident at a first-trimester anatomy evaluation, due to the natural history of fetal malformations, and a second-trimester anatomical survey remains the "gold standard," we will consider some patients who might benefit from first-trimester anatomy ultrasound. Diagnostic performance of first-trimester ultrasound in detecting major fetal structural abnormalities has been

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Table 3.1 Standard indications for first-trimester ultrasound [116]

1.	Confirmation of the presence of an intrauterine pregnancy
2.	Evaluation of a suspected ectopic pregnancy
3.	Defining the cause of vaginal bleeding
4.	Evaluation of pelvic pain
5.	Estimation of gestational (menstrual) age
6.	Diagnosis or evaluation of multiple gestations
7.	Confirmation of fetal cardiac activity
8.	Imaging as an adjunct to chorionic villus sampling, embryo transfer
9.	Localization and removal of an intrauterine device
10.	Assessing for certain fetal anomalies, such as anencephaly, in high-risk patients
11.	Evaluation of maternal pelvic masses and/or uterine abnormalities
12.	Measuring the nuchal translucency (NT) when part of a screening program for fetal aneuploidy
13.	Evaluation of a suspected hydatidiform mole

described as 29–78.8 %, with an overall detection rate of 50 % [17–19]. The highest detection rate of 88–100 % has been reported in acrania, holoprosencephaly, hypoplastic left heart syndrome, omphalocele, megacystis, and hydrops [18]. Scanning in the first trimester may be performed either transabdominally or transvaginally. It was demonstrated that the transvaginal approach is significantly better in visualizing the cranium, spine, stomach, kidneys, bladder, and limbs. Complete fetal anatomy surveys were achieved in 64 % of transabdominal scans and 82 % of transvaginal scans at 13–14 weeks of gestation [20]. Using both transabdominal and transvaginal ultrasonography, noncardiac anatomy was seen in 75 % of fetuses with a crown-rump length of 45–54 mm and in 96 % with a crown-rump length (CRL) of more than 65 mm [21] (Figs. 3.1, 3.2, 3.3, and 3.4).

Maternal Comorbidities

Fetal anomalies may have various etiologies, such as genetic, environmental, or multifactorial. Various maternal conditions and/or their treatment are known to be associated with structural anomalies or restricted growth. Sonographic measurements of fetal ultrasound parameters are the

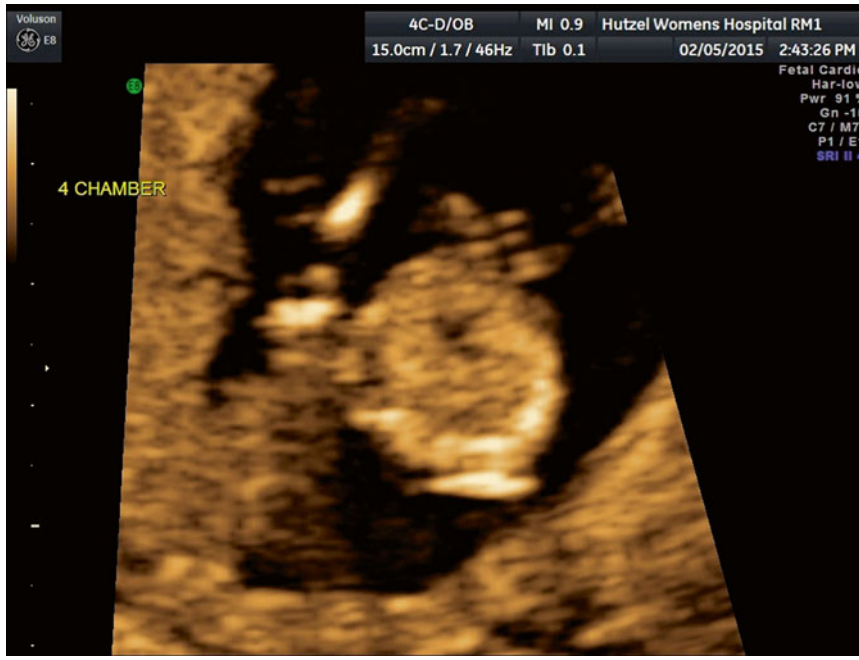

Fig. 3.1 A four-chamber view of the fetal heart at 13 weeks of gestation. Transabdominal approach

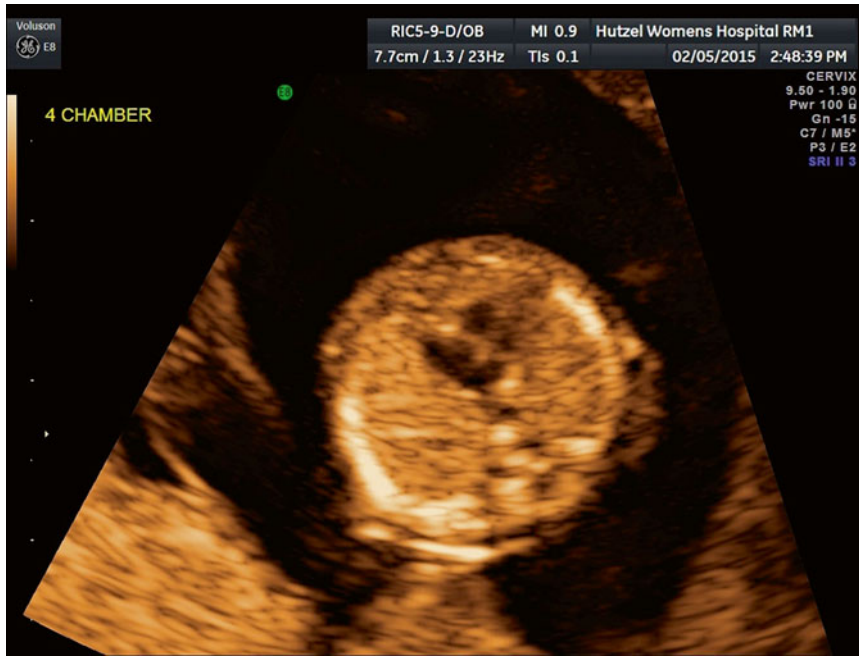

Fig. 3.2 A four-chamber view of the fetal heart at 13 weeks of gestation. Transvaginal approach

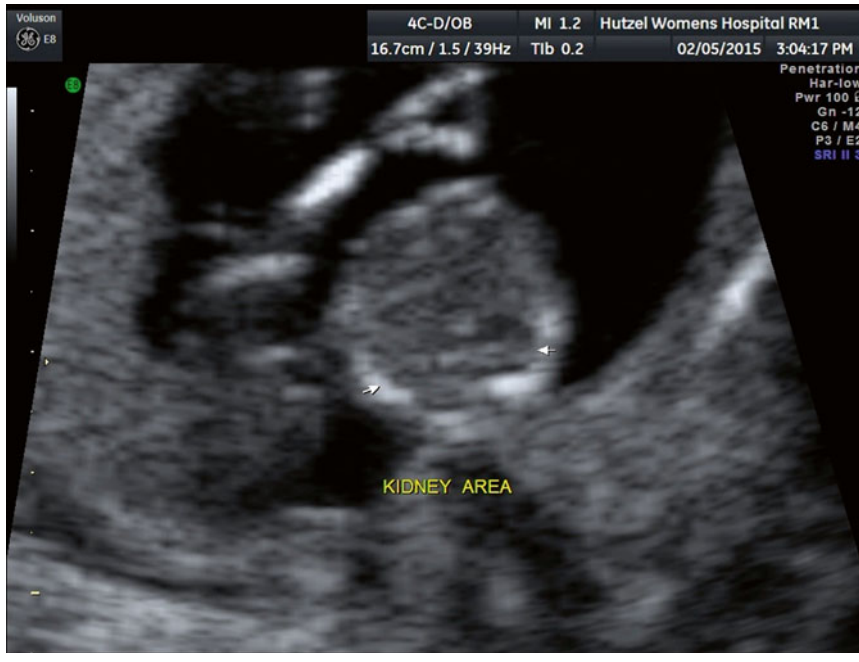

Fig. 3.3 Kidney area of the fetus at 13 weeks of gestation. Transabdominal approach

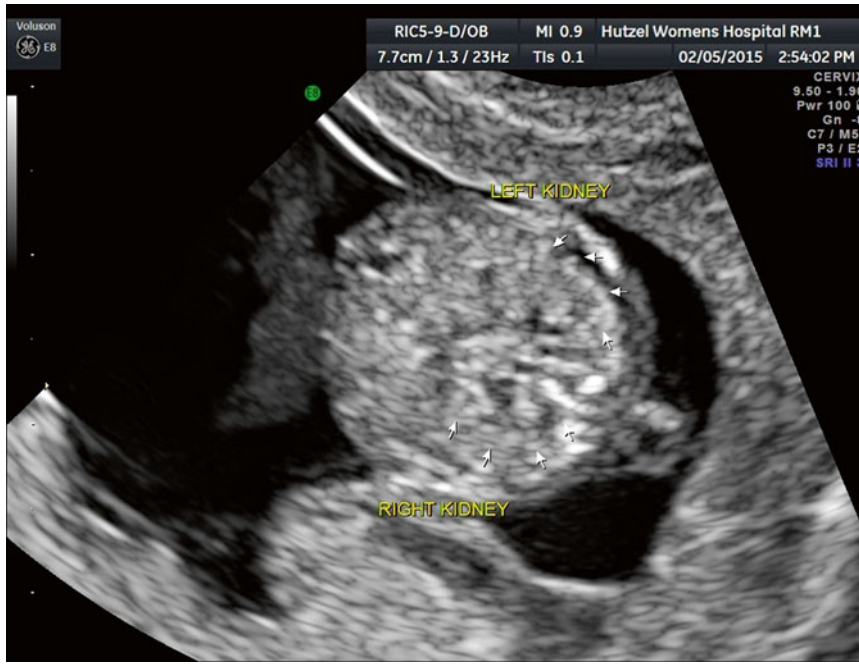

Fig. 3.4 Kidney area of the fetus at 13 weeks of gestation. Transvaginal approach

basis for accurate determination of gestational age and detection of fetal growth abnormalities. Crown-rump length between 7 and 12 weeks is the most accurate parameter for first-trimester dating. First-trimester growth charts and predictive equations based on CRL instead of menstrual dating are more accurate [22]. Gestational age assessment is very important in the diagnosis of fetal conditions that involve early growth abnormalities due to conditions such as maternal hypertension, autoimmune disease, and preeclampsia. Clinical application of fetal biometry in abnormal growth is also important in cases of small- and large-for-gestational-age fetuses, chromosomal aberrations, and skeletal dysplasias.

Pregestational Diabetes

Maternal pregestational diabetes is a well-known risk factor for congenital anomalies. The types of congenital anomalies in diabetic pregnancies differ from those of nondiabetic pregnancies.

The overall incidence of congenital malformations in diabetic pregnancies has been reported to be 6–13 %, which is twofold to fourfold greater than that of the general population [23–25]. A higher proportion of central nervous system (CNS) abnormalities (anencephaly, encephalocele, meningomyelocele, spina bifida, and holoprosencephaly); cardiac anomalies (transposition of the great vessels, ventricular septal defect [VSD], single ventricle, and hypoplastic left ventricle); and kidney anomalies [26–31] are reported. The detection rate for CNS anomalies in the first trimester has been reported to be as high as 100 % in cases of anencephaly and encephalocele and only 18 % in cases of spina bifida [18, 32], because the typical findings of "lemon sign" and "banana sign" do not appear until the end of the first trimester [33, 34].

Obesity is a well-known risk factor for and comorbidity of diabetes. Moreover, several studies reported that women with pregestational diabetes and BMI higher than 28 kg/m^2 have a threefold increase in the risk of congenital anomalies, and the risk further increases proportionally with BMI [35–37]. The potential role of first-trimester anatomy ultrasound in the obese gravida is discussed further below.

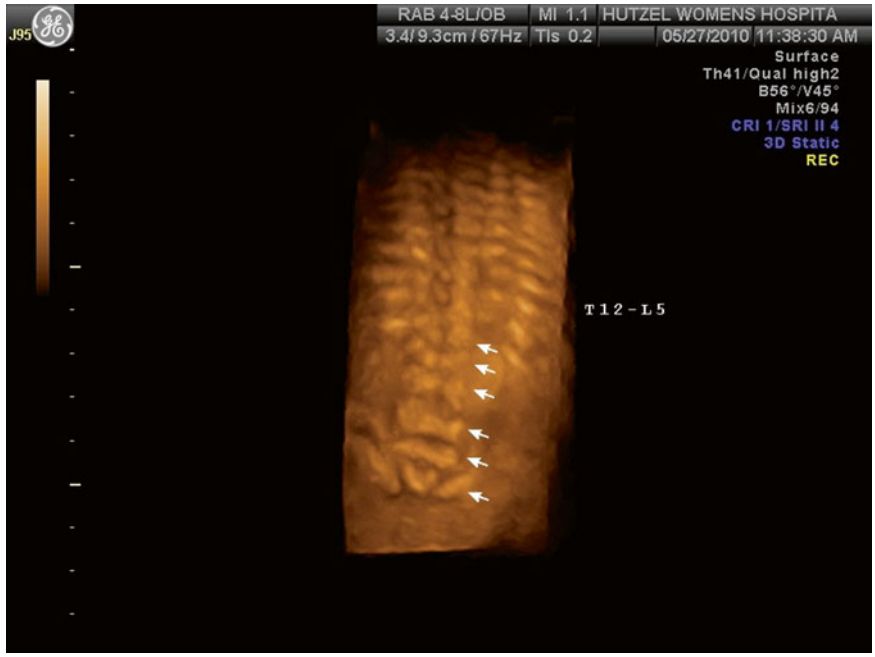

Fig. 3.5 Sacral agenesis in patient with pregestational diabetes

Rates of fetal malformation appear to be similar for type 1 and type 2 diabetes [38]. It is well known that the poorer the glycemic control is periconceptionally or early in pregnancy, the greater the risk is for congenital anomalies [39, 40]. Lack of proper glycemic control during pregnancy is associated with profound fetal anomalies. Maternal hyperglycemia at the time of fertilization (defined as a glycosylated hemoglobin [HbA1c] > 7.5 %) has been associated with a ninefold increase in congenital fetal anomalies and a fourfold increase in spontaneous abortion [41, 42].

Women with pregestational diabetes are advised to plan their pregnancy and optimize the glycemic control before pregnancy. The Canadian Diabetes Association (CDA) and American Diabetes Association (ADA) recommend HbA1c level for pregnancy to be ≤ 7 % before conception is attempted to decrease the risk of congenital malformations [43, 44]. They also encourage the women to take 4–5 mg of folic acid daily, although the evidence suggests that folic acid is more protective against spina bifida than anencephaly and encephalocele [45]. However, unplanned pregnancies occur in 50 % of all pregnancies and the majority of women do not seek prenatal care until after embryogenesis (4–8 weeks of gestation). Thus, we should consider the evaluation of anatomy using first-trimester ultrasound in a pregnancy complicated by pregestational diabetes. Although certain anomalies of the central nervous system may not be detected between 11 and 14 postmenstrual weeks, there have been case reports demonstrating the detection of congenital and major anomalies of the central nervous system using transvaginal ultrasonography in the first trimester [46].

While infants of diabetic mothers are at risk for a wide variety of malformations, one syndrome is strongly associated with diabetes. Caudal regression syndrome (Figs. 3.5 and 3.6) is a condition associated with hypoplastic lower extremities, caudal vertebrae, sacrum, neural tube, and urogenital organs [27, 30, 42]. Sirenomelia (the Mermaid syndrome) has been described as a severe and lethal form of caudal regression sequence and characterized by a single lower extremity, absent sacrum, urogenital anomalies, and imperforate anus. The prevalence of sireno-

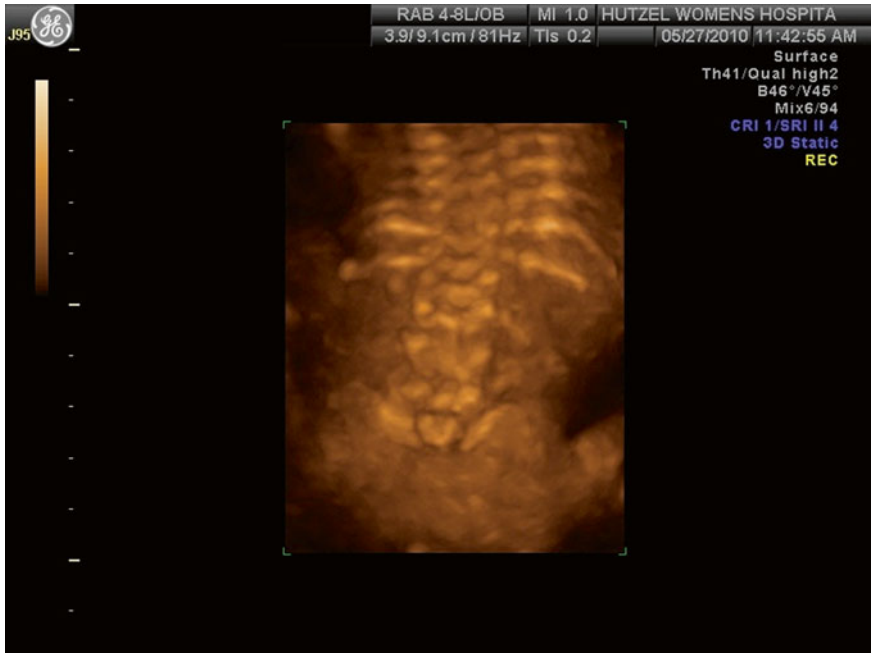

Fig. 3.6 Sacral agenesis in patient with pregestational diabetes

melia has been reported to be 1–3 per 100,000. These malformations occur before the ninth pregnancy week, which has important implications in the prevention of malformations in diabetic pregnancies. The detection of sirenomelia has been described as early as 9 weeks of gestation [47].

A first-trimester anatomy ultrasound may be considered in women with pregestational diabetes in order to detect neural tube defects [NTDs] such as anencephaly and encephalocele, certain cardiac anomalies, and certain limb defects [11, 19].

Obesity

Obesity in pregnancy, defined as maternal prepregnancy body mass index (BMI) of 30 kg/m^2 and extreme obesity with BMI > 40 kg/m^2, are now recognized as a major syndrome in the Western world [48–50]. In the USA, more than 35.8 % of women meet obesity criteria, and its prevalence is increasing steadily among women older than 20 years old, assuming epidemic proportions [51]. It is also associated with an increased risk of congenital anomalies such as cleft palate, neural tube defect and cardiac malformations, hydrocephaly, anal atresia, hypospadias, cystic kidney, pes equinovarus, omphalocele, and diaphragmatic hernia [52–55]. Thus, the ability to adequately visualize these structures at midtrimester prenatal ultrasound examination has significant clinical implications. Antenatal sonographic detection of congenital anomalies is difficult in obese patients. A patient's body mass index significantly affects the ability of the sonographer to achieve a complete anatomical survey. As maternal BMI increases, the rate of completion of anatomic surveys decreases and the number of scans required increases [56]. The detection rate of anomalous fetuses with either standard or targeted ultrasonography decreased by at least 20 % in obese women compared to those with normal BMI [57].

Timor-Tritsch et al. proposed that ultrasound examination, with state-of-the-art equipment and in expert hands, can visualize as many structures at 13–14 weeks as it could at 16 weeks 5–10 years previously, and at 20–22 weeks 15–20 years previously [16]. Hendler et al. found that obesity increased the rate of sub-optimal ultrasound visualization for fetal cardiac and craniospinal

structures and recognized that in these cases it may require visualization of these structures after 18–22 weeks using a transabdominal approach [58]. Gupta et al. recently suggested performing first-trimester fetal anatomic survey in addition to a routine second-trimester anatomy scan to improve the detection rate of congenital anomalies in obese patients [59]. Transvaginal sonography bypasses the maternal abdominal adipose tissue and the late first-trimester transvaginal scan may be the only opportunity to visualize the fetal anatomy adequately in the obese pregnant patient [60].

Maternal Conditions Associated with Congenital Heart Defects

Various teratogenic agents and maternal conditions have been implicated as the etiologic agents of congenital heart disease [CHD] (see also Chap. 4). Maternal pregestational diabetes has 2–5 times the risk of CHD. Anomalies, such as transposition of the great arteries, truncus arteriosus, visceral heterotaxy and single ventricle, are more common among offspring of diabetic mothers compared to women without diabetes [28, 61–64]. Ventricular septal defect and transposition of the great arteries are the most common cardiac defects in fetuses of diabetic mothers [61]. Establishing glycemic control before and early in pregnancy improves maternal and fetal outcomes, including reduction of CHD [65–67].

Overall, CHD is the most common congenital anomaly, with an incidence of 6–8 % of all live births, accounting for 30–45 % of all congenital defects [68–70]. Prenatal diagnosis of CHD may be used to optimize care and potentially be lifesaving [71–73]. Fetal echocardiogram at 18–20 weeks gestation is a well-established method for evaluation of fetal cardiac structure and function. With improved technology, it has become feasible to obtain images of the fetal heart as early as 11 weeks gestation [14, 74]. Moreover, there is mounting evidence that an increased NT is associated with major cardiac defects in the fetus and therefore represents an indication for specialized fetal echocardiography [75–77]. A recent meta-analysis showed that the use of the 99th centile (i.e., 3.5 mm) can identify around 30 % of fetuses with CHD, supporting the notion that NT is the strongest predictor of CHD in the first trimester [75]. Abnormal ductus venosus (DV) blood velocity waveform (absent or reverse A-wave) in the first trimester has also been associated with increased risk for adverse perinatal outcome, in particular for chromosomal anomalies and CHD [78, 79] (Figs. 3.3, 3.4, 3.5, 3.6, and 3.7). Abnormal DV blood velocity waveform in the first trimester is an independent predictor of CHD and should constitute an indication for early echocardiography. It has been reported that the use of DV blood velocity assessment increased early detection of CHD by 11 % with respect to the use of NT measurement alone [80]. The combined data from eight studies on euploid fetuses with increased NT (above the 95th centile) demonstrated abnormal DV blood velocity waveform in 87 % of fetuses with cardiac defects, compared with 19 % without cardiac defects [81]. Thus, many groups have suggested the use of DV as a secondary marker to be assessed selectively in fetuses with increased NT [82–84].

Several studies have shown that complete evaluation rate of the heart increased from 45 % at 11 weeks to 90 % between 12 and 14 weeks and 100 % at 15 weeks [12, 13, 85]. The visualization of the four-chamber view and the cross-over of the pulmonary artery and aorta have been reported from 44 % at 10 weeks to 100 % at 13–17 weeks [12]. Transvaginal echocardiography is reported to be superior to the transabdominal approach between 10 and 13 weeks of gestation, both methods are similar at 14 weeks of gestation, and transabdominal echocardiography is more accurate than transvaginal at 15 weeks of gestation [85]. Detection of cardiac anomalies in the first trimester varies by lesion, as noted in Tables 3.2 and 3.3.

Phenylketonuria (PKU) is another metabolic disorder that is associated with CHD. Women with PKU who have elevated phenylalanine levels are at increased risk for offspring with CHD. VSD and coarctation of the aorta are most common in this population [86]. Levels exceeding 15 mg/ml are associated with a 10- to 15-fold increase in CHD [87]. The etiology of CHD is related not

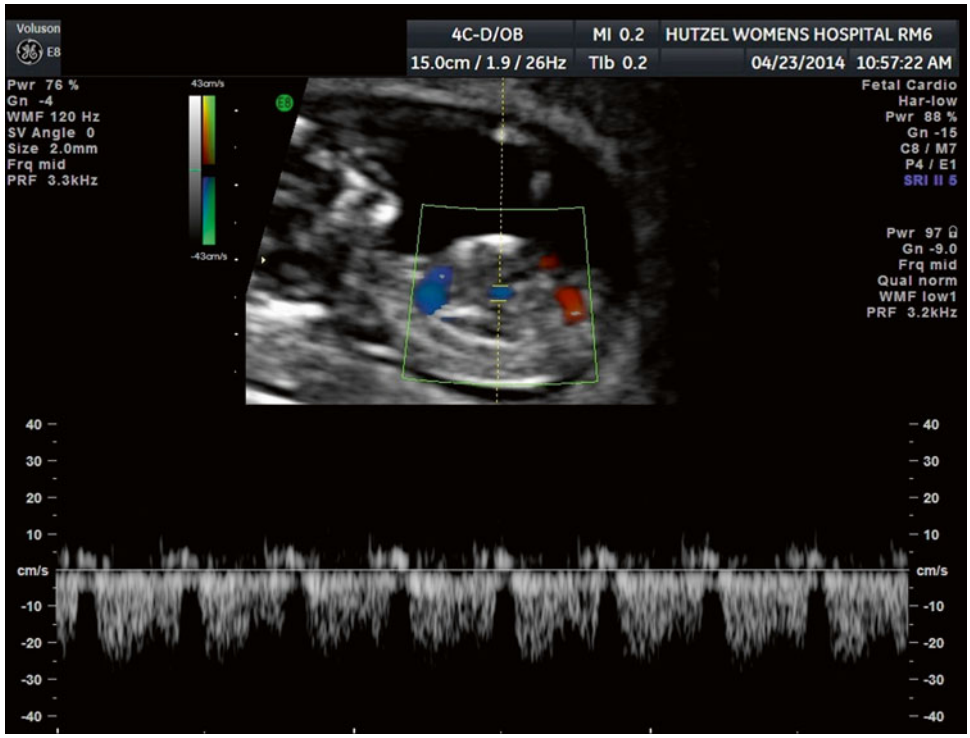

Fig. 3.7 Abnormal ductus venosus (DV) blood velocity waveform at 12 weeks of gestation

Table 3.2 Cardiac lesions that may be detected in the first trimester [117]

1. Tricuspid atresia
2. Pulmonary atresia (with or without ventricular septal defect [VSD])
3. Mitral atresia
4. Aortic atresia
5. Hypoplastic left heart syndrome (aortic and mitral atresia or severe stenosis)
6. Complete transposition
7. Corrected transposition
8. Double inlet ventricle
9. Atrioventricular septal defect (large septal defects)
10. Truncus arteriosus
11. Tetralogy of Fallot
12. Large ventricular septal defects
13. Complex lesions in the setting of laterality defects

Table 3.3 Cardiac lesions that may be overlooked in the first trimester [117]

Developmental lesions
1. Mild aortic/pulmonary stenosis
2. Mild mitral/tricuspid valve abnormalities
3. Coarctation of the aorta
4. Cardiac tumors
5. Cardiomyopathies
Septal defects
1. Ventricular septal defects
2. Primum atrial septal defects
3. Atrioventricular septal defects
Others
1. Tetralogy of Fallot with normal size pulmonary arteries
2. Abnormalities of pulmonary venous return

only to elevated blood phenylalanine levels, but also to poor protein and vitamin intake during the first trimester [88]. Diet control before conception and during pregnancy has shown reduced risk of CHD [89, 90].

Anticonvulsants, a class of drugs that includes phenytoin, carbamazepine and sodium valproate, are commonly used in the treatment of epilepsy. The incidence of congenital defects is 4–10 %, an approximate twofold to fourfold increase compared to the general population

[91–97]. Polytherapy with antiepileptic drugs (AEDs) is associated with a higher malformation rate than monotherapy [98]. Use of certain AEDs during pregnancy increases the risk for specific congenital malformations, such as neural tube defects, cleft lip and palate, and cardiovascular malformations [99–102]. Valproic acid monotherapy, among the different regimens, has the highest risk of congenital abnormalities in offspring [94]. The use of valproate and carbamazepine is strongly associated with NTDs, especially with spina bifida. The prevalence of spina bifida is approximately 1–2 % with valproate exposure and 0.5 % with carbamazepine [103].

Carbamazepine exposure is associated with Tetralogy of Fallot, esophageal atresia, vertebral anomalies, and multiple terminal transverse limb defects [97]. The most common cardiac anomalies reported among offspring exposed to carbamazepine are VSD, Tetralogy of Fallot, patent ductus arteriosus (PDA) and atrial septal defect (ASD) [97, 100, 104, 105]. In light of these results, we should consider first-trimester anatomy ultrasound and fetal echocardiogram for women with epilepsy on AEDs.

Alcohol abuse during pregnancy is associated with health problems to both mother and fetus.

Of the four million pregnancies in the USA each year, 3–5 % of women drink heavily throughout pregnancy [106]. The fetal alcohol syndrome (FAS) is considered to be the most severe manifestation of the adverse effects of alcohol on the fetus. A diagnosis of FAS requires prenatal alcohol exposure and the following characteristics: fetal growth restriction, neurocognitive delays and/or mental retardation, and at least two facial dysmorphic features (short palpebral fissures, thin vermillion border, or smooth philtrum) [107]. FAS occurs in 4–10 % of children born to alcoholic mothers. CHD is reported in 25–50 % of infants with FAS; ASD and VSD are the most common [108–110]. The findings suggest that prenatal alcohol exposure as a potential etiology of CHD may also be considered as an indication for performing first-trimester fetal echocardiogram.

Maternal Vascular Disease

Women with hypertension, renal disease, and vascular disease have a recognized increased risk of preeclampsia, fetal growth restriction, and other adverse pregnancy outcomes. While most of these women will be candidates for low-dose aspirin therapy, identification of a particularly high-risk subset may allow more intensive surveillance and targeted interventions. Abnormal placental vascular development is a basis of common obstetrical disorders such as fetal growth restriction and preeclampsia. Uterine artery Doppler has been investigated as a predictive and diagnostic tool.

It has been reported that pregnancies with an increased risk of developing hypertensive disorders and related complications have an abnormally increased UtA-PI in early pregnancy [111]. The 11- to 14-week period is characterized by an elevated UtA-PI and bilateral notching. As pregnancy progresses, UtA-PI decreases and bilateral notching is less prevalent [112, 113]. A meta-analysis involving 55,974 women has shown that first-trimester uterine artery Doppler is a useful tool for predicting early-onset preeclampsia, as well as other adverse pregnancy outcomes [114]. Aspirin treatment initiated before 16 weeks of pregnancy may reduce the incidence of preeclampsia and its consequences in women with ultrasonographic evidence of abnormal placentation diagnosed by first-trimester uterine artery Doppler studies [115].

Summary

First-trimester ultrasound is already a common part of our obstetric armamentarium. As our patients, their comorbidities, and the sophistication of ultrasound change, so too may we change our approach to prenatal diagnosis. While the information presented here does not reflect current standard of care, we anticipate further evolution of condition- and exposure-based recommendations, including first-trimester anatomy studies and echocardiography in selected populations.

Teaching Points

- Ultrasound performed in the first trimester confirms an intrauterine pregnancy, establishes accurate dates, pregnancy failure, and ectopic pregnancy.
- It is also used for risk assessment for aneuploidy, through measurement of nuchal translucency and identification of the presence or absence of the nasal bone.
- Complete fetal anatomy surveys can be achieved in 64 % of transabdominal scans and 82 % of transvaginal scans at 13–14 weeks of gestation. This helps to shift the prenatal diagnosis from the standard second-trimester anatomy scan into the first trimester.
- Various maternal conditions and/or their treatment are known to be associated with structural anomalies or restricted growth. Maternal pregestational diabetes is a well-known risk factor for congenital anomalies. The overall incidence of congenital malformations in diabetic pregnancies is 6–13 %, which is twofold to fourfold greater than that of the general population.
- Obesity is a well-known risk factor for and comorbidity of diabetes. Women with pregestational diabetes and BMI higher than 28 kg/m^2 have a threefold increase in the risk of congenital anomalies, and the risk further increases proportionally with BMI.
- Congenital heart disease (CHD) is the most common congenital anomaly, with an incidence of 6–8 % of all live births, accounting for 30–45 % of all congenital defects. An increased nuchal translucency (NT) and/or abnormal ductus venosus (DV) blood velocity waveform are associated with major cardiac defects in the fetus. Complete evaluation rate of the heart increased from 45 % at 11 weeks to 90 % between 12 and 14 weeks and 100 % at 15 weeks.
- Maternal metabolic diseases such as PKU and diabetes, and exposure to certain medications such as anticonvulsants are associated with CHD. These conditions might be considered as an indication for performing first-trimester fetal echocardiogram.
- First-trimester uterine artery Doppler is a useful tool for predicting early-onset preeclampsia, as well as other adverse pregnancy outcomes. Aspirin treatment initiated before 16 weeks of pregnancy may reduce the incidence of preeclampsia and its consequences in women with ultrasonographic evidence of abnormal placentation diagnosed by first-trimester uterine artery Doppler studies.

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First-Trimester Embryology: An Overview

4

Cresta W. Jones, Deborah Penzkover, Rachel Pollard, and Randall S. Kuhlmann

Introduction

Normal human development is a continuum. In particular, the first-trimester pregnancy development is a period of rapid progression from a fertilized egg to an embryo with a clearly identified human form. Interruptions in this ongoing process can result in abnormal development and subsequent congenital anomalies. These anomalies can be the result of many etiologic factors (Table 4.1) [1]. Approximately 3 % or greater of pregnancies are complicated by congenital anomalies, and it is anticipated that many of these anomalies will be identified by prenatal ultrasound, often in the first trimester. The purpose of this chapter is to provide the clinician or sonographer with the essential basics of embryological and fetal development, to better understand mechanisms of normal and abnormal first-trimester human development. Understanding of these mechanisms is imperative for adequate evaluation of the first-trimester fetus in the ultrasound laboratory.

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Signaling Pathways Identified for Normal Embryo Development

Embryonic development in the first trimester is extensive, with a small group of totipotent (able to differentiate into any cell within the organism) stem cells located in the inner cell mass of the blastula responsible for cellular differentiation and subsequent organ formation. It is important to be aware that this complex formation appears to be controlled by *cell signaling* pathways, which guide normal development both by the location of their expression as well as the specific time at which they are active in the embryo and surrounding tissues. Detailed descriptions of all signaling pathways are beyond the scope of this chapter, but are well described in other texts [2–6].

Development of the Bilaminar Embryo (Weeks 1–2)

After successful fertilization, the resulting zygote quickly undergoes cleavage to rapidly progress through the blastula and morula stages. The morula

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Table 4.1 Causes of malformations in fetuses/infants[a]

Chromosomal	10.0 %
Single gene	3.0 %
Familial	14.5 %
Multifactorial	23.0 %
Teratogens	3.2 %
Uterine anomalies	2.5 %
Twinning	0.4 %
Unknown	43.2 %

[a]Based on data from ref. [1]

will separate into an inner cell mass (the embryoblast, or future embryo) and an outer cell mass (the trophoblast component of the placenta).

The embryoblast differentiates into a *bilaminar embryonic disc*, consisting of dorsal epiblast and ventral hypoblast. This typically occurs around day 14 after fertilization, around the time of completion of implantation [6]. A new layer of cells is derived from the epiblast, the extraembryonic mesoderm, and proceeds to aid in the origins of extraembryonic components such as the amniotic cavity and the umbilical vesicle.

Embryonic Weeks 3–4

During this period, all the major organ systems of the embryo and fetus will begin to develop. During the third week of embryonic development (5 weeks after the last menstrual period), the most notable processes include the development of the primitive streak and notochord [7], and the creation of the three germ layers of the *trilaminar embryonic disc* (Fig. 4.1).

The process of *gastrulation* results in the development of the three critical germ layers of the human embryo—endoderm, ectoderm, and mesoderm [8]. From these three simple layers will develop all fetal tissues and organs (Fig. 4.2). In addition, gastrulation marks the beginning of *morphogenesis*, the shaping of an organism by the differentiation of cells, tissues, and organs and organ systems, according to its genetic direction [9].

During this time, the *primitive streak* develops (Fig. 4.3) and will give rise to the primitive node. This is critical to allow the development of mesenchyme, which will go on to serve as the progenitor for many supporting tissues of the fetus. Although the totipotent cells of the primitive streak typically regress by 4 weeks of development, remnants are believed to lead to the formation of a unique fetal tumor, the *sacrococcygeal teratoma* [10]. Newly formed mesenchyme will migrate through the streak and become a chord of tissue known as the *notochord*. The notochord determines the axis of the embryo and becomes a rod-like support for further axial development. Through signaling pathways that include sonic hedgehog (Shh) and bone morphogenetic proteins (BMPs), the *notochord* and overlying developing neural tube will orchestrate the establishment of the axial central nervous system and axial musculoskeletal system, as well as the segmentation of the nervous system [11]. Furthermore, the paraxial mesoderm (mesoderm located on each side of the developing neural tube) divides into intermediate and lateral mesoderm, which will give rise to components of the musculoskeletal system and the urinary tract [6].

Formation of the Neural Tube

This critical component of embryonic development begins during the fourth embryologic week. As the notochord develops, signaling pathways induce the formation of the neural plate, which will give rise to the future brain and spinal cord. The neural plate becomes a groove and subsequently folds begin to form, a process known as *neurulation* [12]. Fusion of the neural groove into the neural tube occurs in a zipper-like fashion, beginning in the midline and progressing in both cranial and caudal directions. Non-fusion at any site is known as *spina bifida*, which can range from small defects that are functionally unimportant (*spina bifida occulta*) to severe defects, which are incompatible with life such as *anencephaly* (Fig. 4.4) [13].

During the development of the neural tube, *neural crest* cells are differentiating as columns of cells along both sides of the neural tube. These cells are critical to normal embryonic development, as they migrate throughout the embryo to

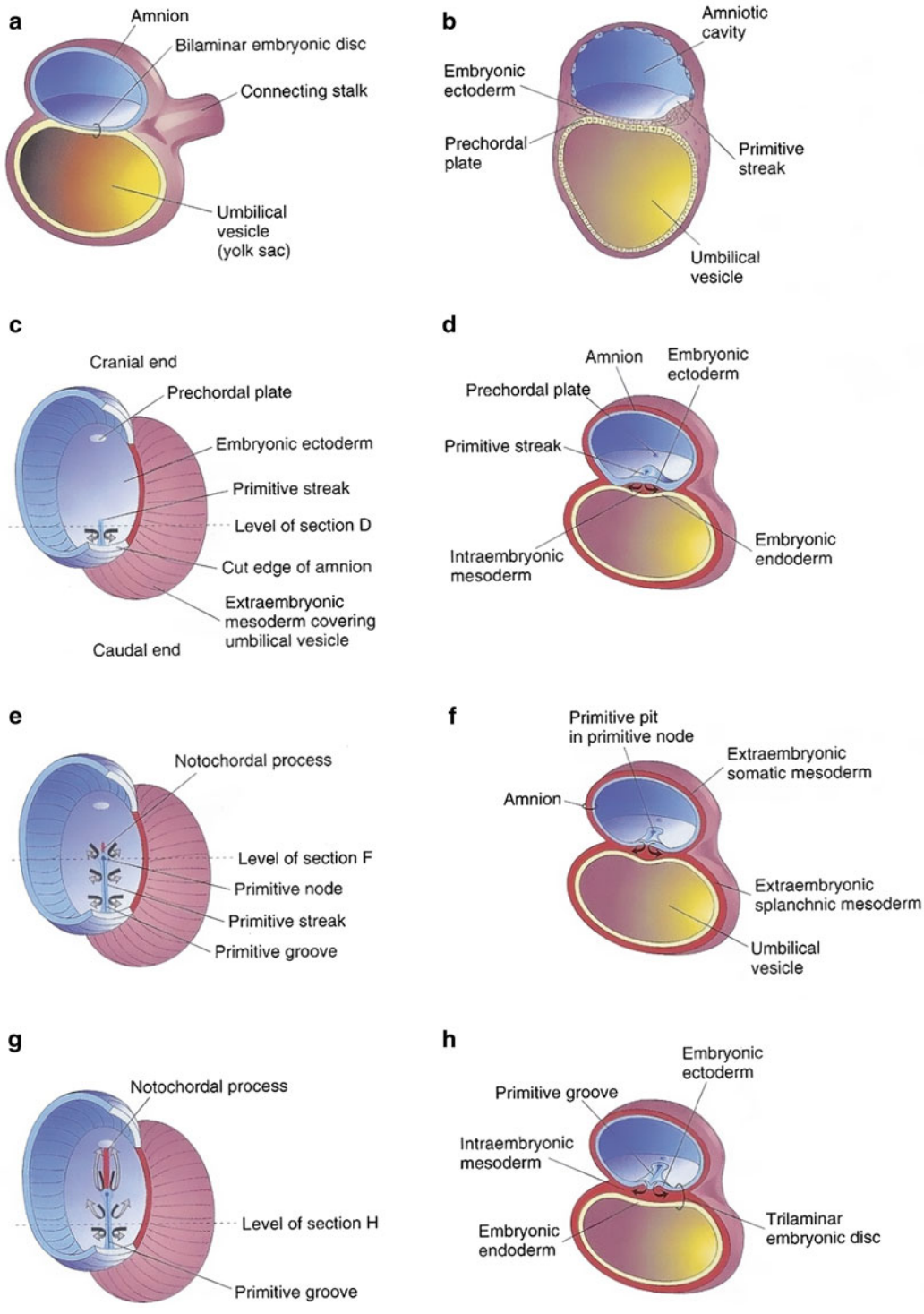

Fig. 4.1 The formation of the trilaminar embryonic disc. The *arrows* indicate invagination and migration of mesenchymal cells from the primitive streak. (**c**, **e**, **g**) Dorsal views of the trilaminar disc early in week 3, exposed by removal of the amnion. (**a**, **b**, **d**, **f**, **h**) Transverse sections through the embryonic disc, with the level of each section indicated in (**c**), (**e**), and (**g**). This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

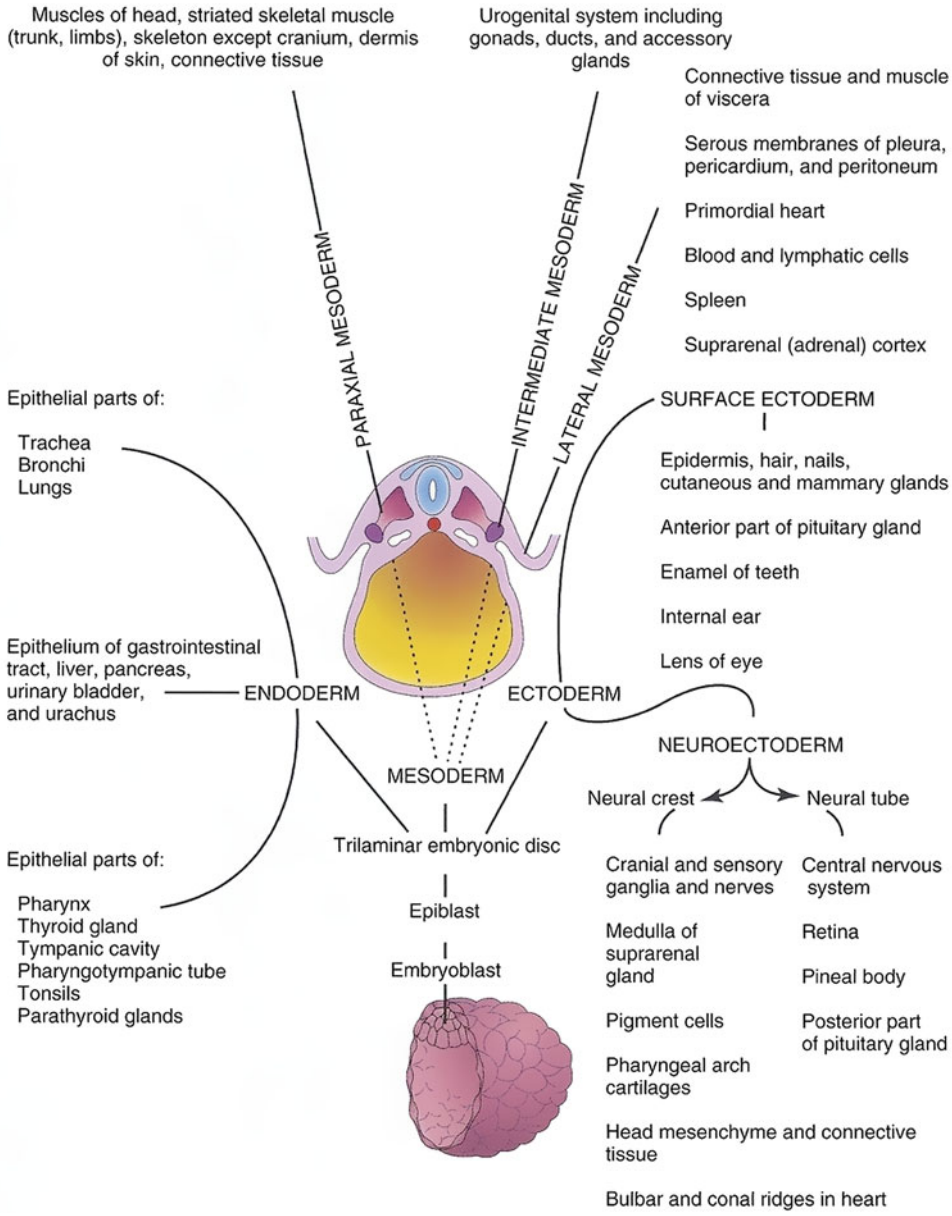

Fig. 4.2 Schematic of the derivatives of the three germ layers of the trilaminar embryonic disc: ectoderm, endoderm, and mesoderm. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

give rise to components of the heart, head and face, and to ganglia of the spine and autonomic nervous system, pigment cells, adrenal glands, and the medulla [14]. Abnormal development and or migration of the neural crest cells are believed to influence the development of such disorders as *neurofibromatosis* and *CHARGE association* [15].

Embryonic Weeks 5–8

After the formation of the neural tube, the embryo enters a period in which many major external and internal body structures are developed. This period extends from the fifth to eighth week of embryonic development (7–10 postmenstrual weeks) [6].

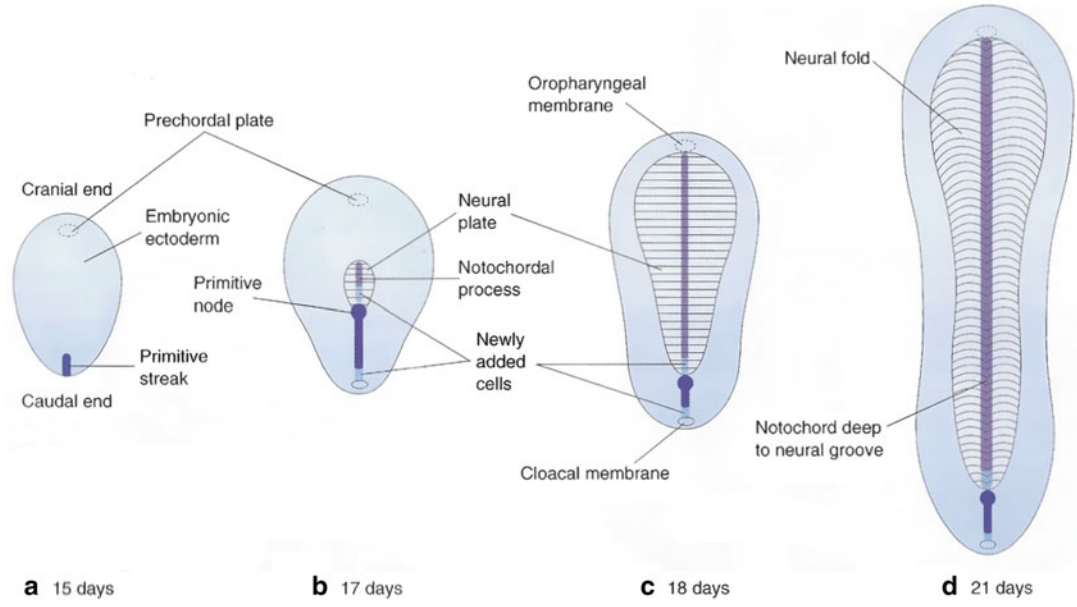

Fig. 4.3 Development of the primitive streak and notochord. The embryo begins to length and change shape in the third embryonic week. The primitive streak lengthens by adding cells at its caudal end, while the notochord lengthens by migration of cells from the primitive node. The notochordal process and adjacent mesoderm induce overlying ectoderm to form the neural plate, which is the embryonic basis of the central nervous system. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

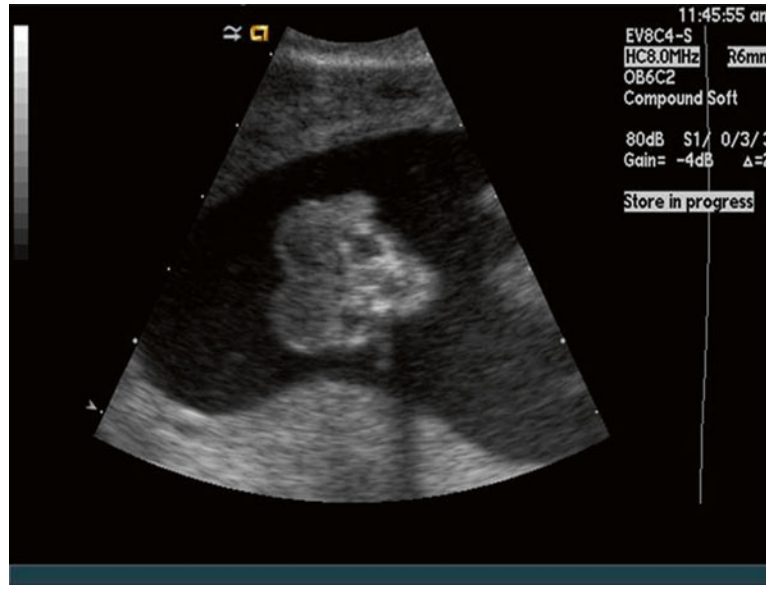

Fig. 4.4 Ultrasound image at 12 week gestation, with anencephaly, a lethal abnormality in which a large portion of the fetal brain is absent, as is the superior portion of the fetal skull, due to incomplete closure of the rostral neuropore during spinal cord formation. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

This critical phase of development is the time at which the conceptus is most vulnerable to teratogens potentially leading to abnormal development. Unfortunately, it is also a time at which many women might not yet be aware that they are pregnant, and thus exposure to environmental agents, which might alter embryonic development, may be increased. Individual organ systems and structures, as formed during the first trimester, are now addressed individually.

Division of the Embryonic Cavities and Diaphragm

The primordium of the body cavities, or intraembryonic coelom, is divided into cavities during the fourth and fifth week. These include the pericardial cavity, two pericardioperitoneal cavities and a single peritoneal cavity. As the fetus begins to fold cranially, the heart and pericardial cavity are located near the developing foregut, and remain in direct communication with the paired pericardioperitoneal cavities [6]. As development continues the peritoneal cavity will become isolated, and fusion and expansion of the remaining cavities will establish separate pleural and peritoneal cavities, and will contribute to the creation of the diaphragm. Development of the definitive diaphragm, which is also occurring at this time, is dependent on coordinated development of four separate components: the pleuroperitoneal membranes, the mesentery of the developing esophagus, muscular ingrowth from the lateral body wall, and the septum transversum, an outgrowth from the dorsal body wall (Fig. 4.5) [16]. Defects in any of these components can result in a congenital diaphragmatic hernia, which is most often caused by defective formation or fusion of the pleuroperitoneal membranes with the other three parts of the diaphragm, and occurs on the left side of the fetus in up to 90 % of cases [17].

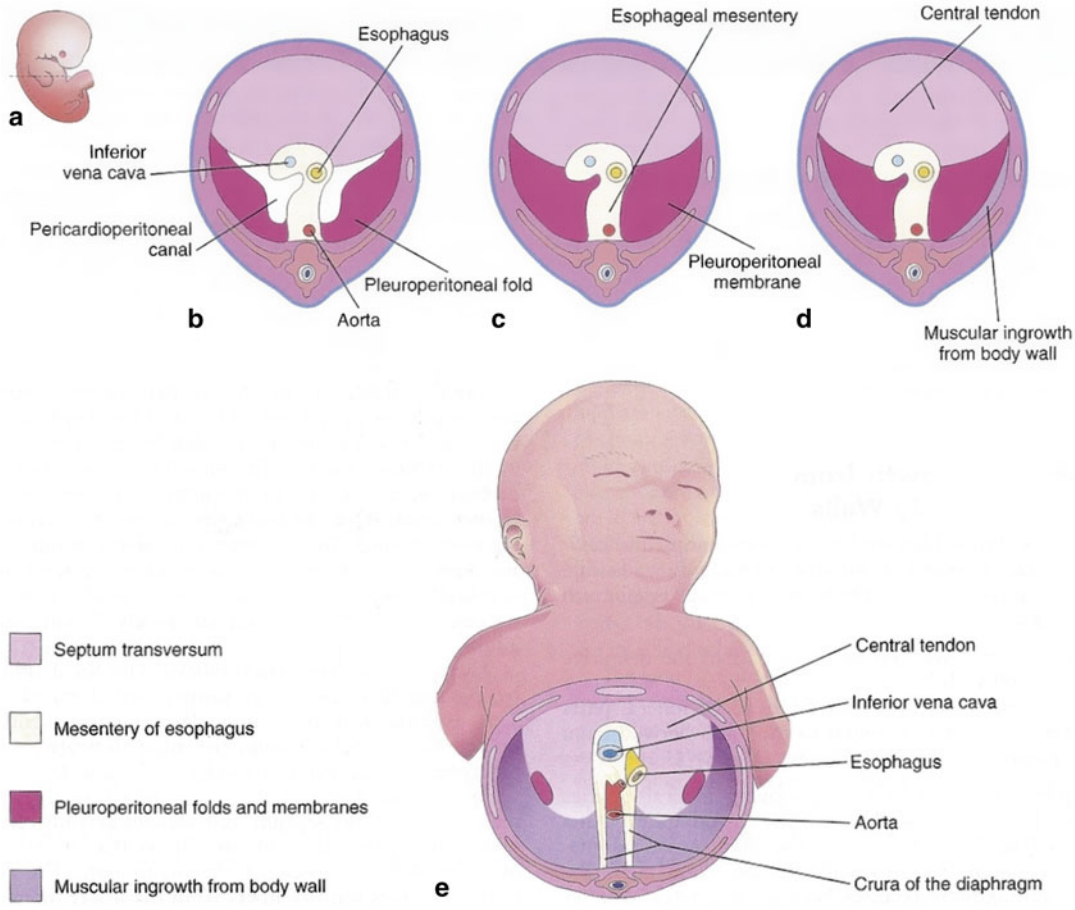

Fig. 4.5 Development of the diaphragm. (**a**) Lateral view of the embryo at the end of the fifth embryonic week, indicating the level of the transverse sections in (**b**), (**c**), and (**d**). (**b**) Transverse section of the pleuroperitoneal membranes prior to fusion. (**c**) Similar section at the end of the sixth embryonic week. (**d**) Transverse section at 12 embryonic weeks. (**e**) Inferior view of the diaphragm in a neonate, identified the embryologic origin of its components. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

Development of the Fetal Face

The development of the fetal face begins with embryonic primordial around the developing fetal mouth or stomodeum. Facial development is dependent on the formation of five structures: frontonasal prominences, maxillary prominences, and mandibular prominences. Appropriate migration and fusion are vital to allow for normal facial and palatal development (Fig. 4.6) [18].

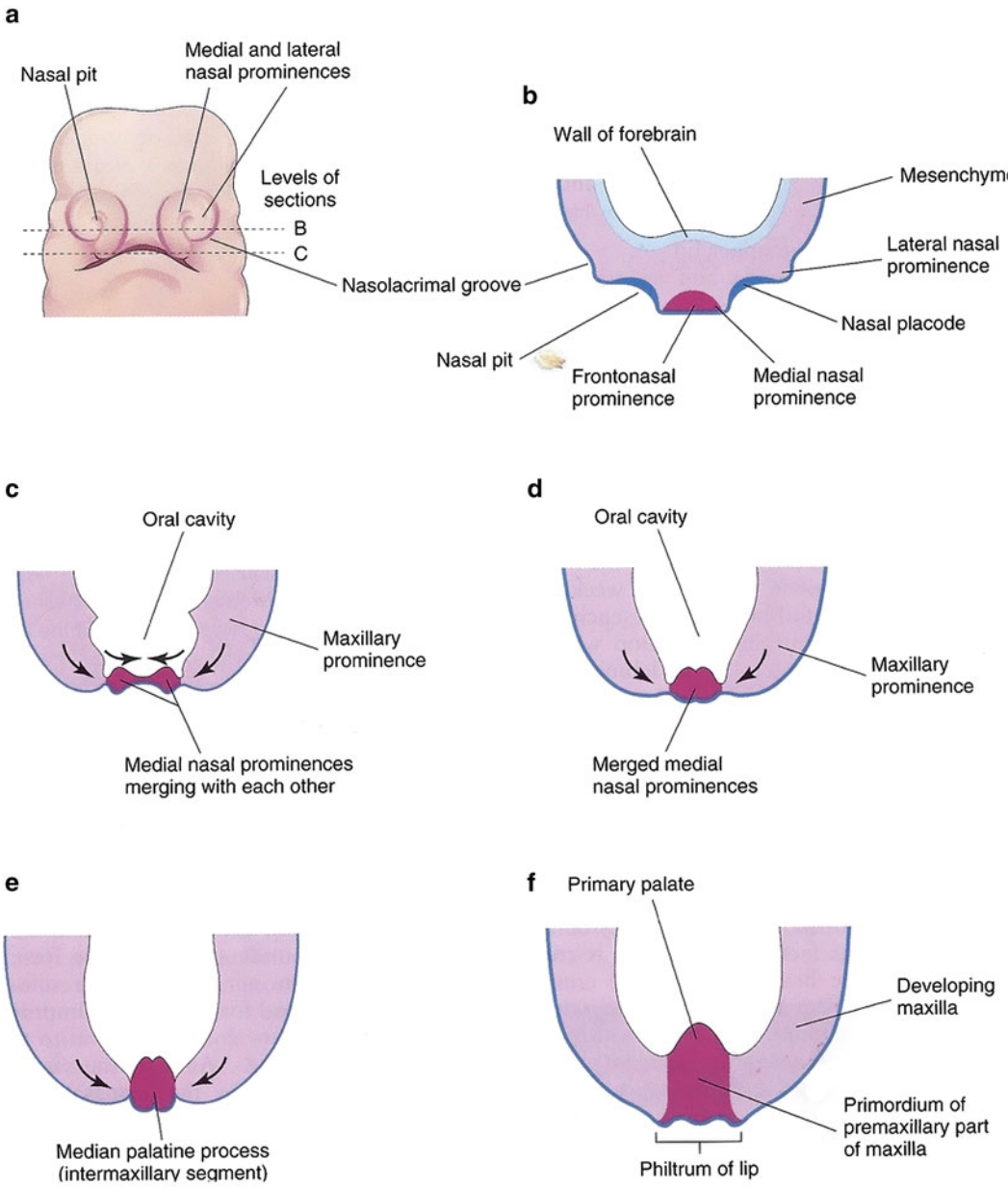

Fig. 4.6 Early development of the maxilla, palate and upper lip. (**a**) Facial view of a fifth embryonic week embryo. (**b**, **c**) Horizontal sections at the levels shown in (**a**). The *arrows* in (**c**) indicate growth of the maxillary and median nasal prominences. (**d**–**f**), Similar sections of older embryos identifying merging of the medial nasal prominences and maxillary prominences to form the upper lip. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

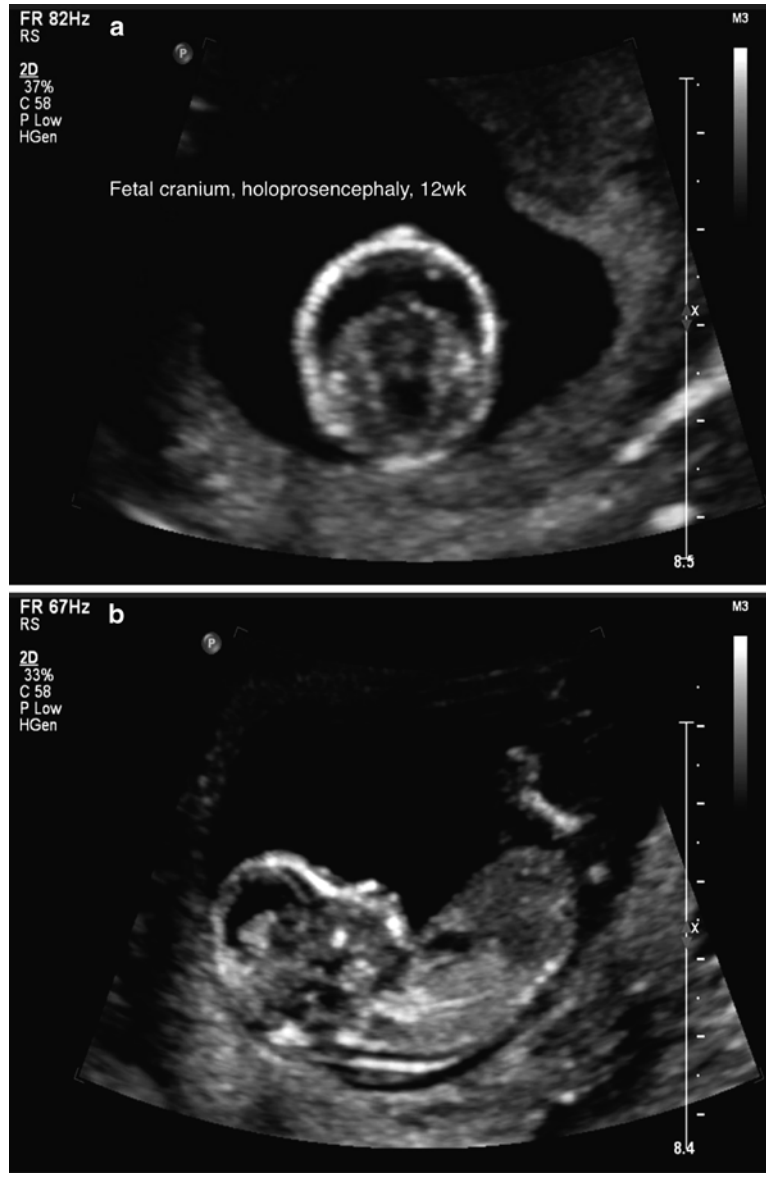

Fig. 4.7 Ultrasound scan of a fetal face at 12 weeks gestation with holoprosencephaly (**a**) and flattened facial profile (**b**) suggestive of severe facial clefting, which was identified in the second trimester. This fetus was ultimately diagnosed with trisomy 13 and midline facial clefting. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

Abnormalities in these processes can result in cleft lip and cleft palate or more severe major clefting of the fetal face. Clefting can also be associated with other midline anomalies such as holoprosencephaly, often due to inappropriate signaling to allow normal component migration and fusion. Such facial hypoplasia is often seen in trisomy 13 (Fig. 4.7a, b).

Development of the Respiratory System

The respiratory system also begins to develop during the fourth embryonic week, as the respiratory diverticulum buds from the primitive foregut. Subsequent migration of splanchnic mesoderm over the diverticulum results in the

development of respiratory buds, which will further divide and differentiate over the course of fetal development. An important step in the respiratory system's formation is the separation of the foregut and esophagus from the trachea through the development of the tracheoesophageal folds, which will fuse to form the tracheoesophageal septum [6]. Inappropriate or incomplete development of this septum can result in various types of tracheoesophageal fistulae (TEF). This abnormal passage is associated with incomplete formation of the esophagus (esophageal atresia) in 85 % of cases [6] and can lead to ultrasound findings of excess amniotic fluid, as the fetus is unable to swallow and assimilate appropriately during gestation [19].

Development of the Gastrointestinal Tract

The primordial gut tube begins to form in the fourth embryonic week as a portion of the yolk sac is incorporated into the embryo as it folds. Initially cell proliferation will obliterate the lumen of the tube, which will then recanalize and differentiate into foregut, midgut, and hindgut components [6]. Incomplete recanalization can result in subsequent areas of stenotic or atretic intestine [20]. The foregut is divided into the trachea and esophagus as addressed in the previous section. Additional components of the foregut include the stomach, which will dilate and rotate to its normal physiologic location in the left upper quadrant, as well as the liver and duodenum [21].

At approximately the sixth embryonic week, the midgut forms a U-shaped loop, which will herniate through the umbilical ring of the embryo, causing physiologic gut herniation, which is a normal step in embryonic development (Fig. 4.8). The loop will rotate 270°, allowing for hernia reduction by embryonic week 11. Abnormalities in hernia reduction can result in persistent bowel herniation into a sac at the umbilical cord insertion in the fetal abdomen, known as omphalocele (Fig. 4.9a, b). Omphaloceles are associated with an increased risk of fetal aneuploidy [22]. This contrasts with gastroschisis (Fig. 4.10a, b), which is defined by a defect located to the right of the umbilicus. Subsequently, the bowel and other structures are allowed to herniate through this defect. The etiologies speculated for this defect include agenesis of the right omphalomesenteric artery, or early disappearance of the right umbilical vein resulting in non-fusion of the lateral folds

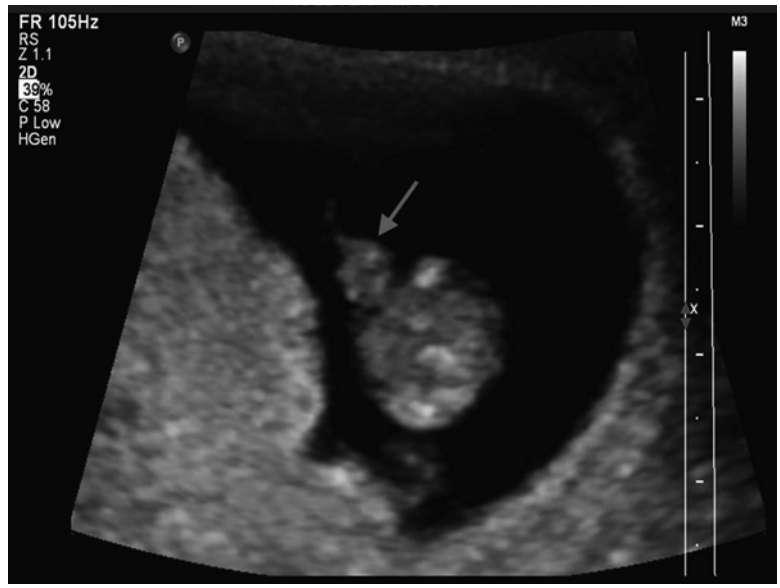

Fig. 4.8 A transverse ultrasound image at 10 weeks through the fetal abdomen demonstrates normal physiological gut herniation. The *arrow* indicates area of herniation. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

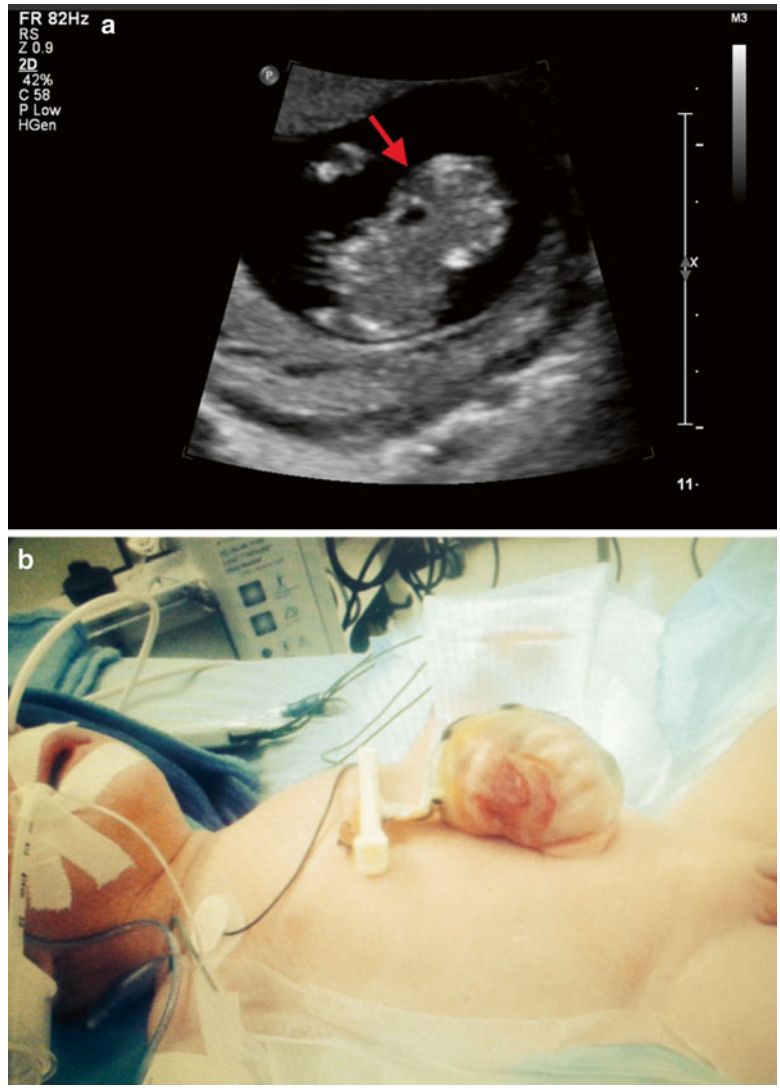

Fig. 4.9 (**a**) Ultrasound at 13 weeks, transverse fetal abdomen with *arrow* indicating large omphalocele. (**b**) Neonate with an omphalocele. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

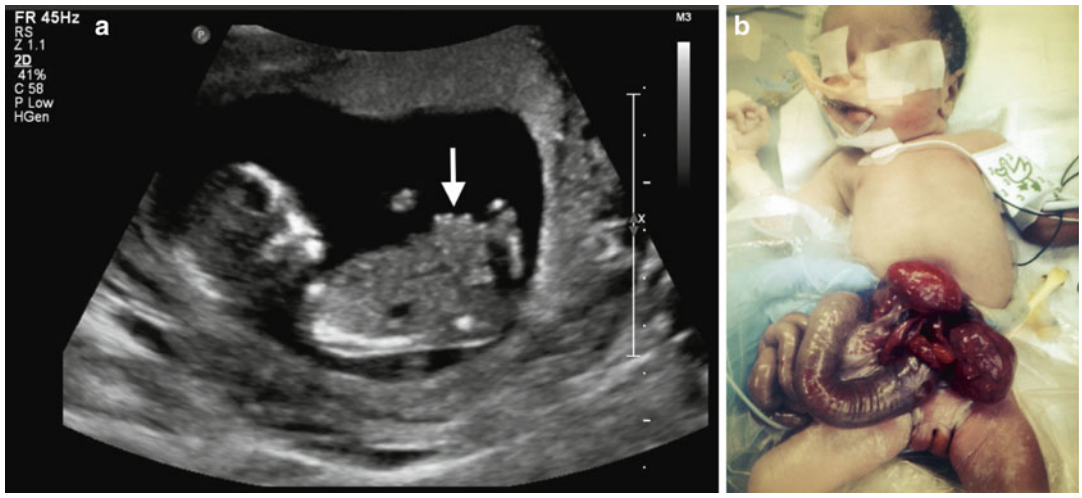

Fig. 4.10 (**a**) Ultrasound at 12 weeks, longitudinal fetus with *arrow* indicating gastroschisis. (**b**) Neonate with gastroschisis. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

of the embryo [6]. Some authors feel that this may represent a ruptured omphalocele. Gastroschisis is typically not associated with an increased risk of fetal genetic abnormalities [23].

Development of the Urogenital System

The fetal renal system progresses through three separate functioning kidney structures [6]. All three have their origins primarily from intermediate mesoderm, which develops into the nephrogenic cord. The initial fetal renal structure, the pronephros, disappears by week 5 of embryonic life. It is replaced by the mesonephros and mesonephric (Wolffian) duct, which will play a critical role in development of the male reproductive system. At 10 embryonic weeks, the permanent renal structure, the metanephros is functional. It develops from an outgrowth of the mesonephros (ureteric bud), and this bud induces the formation of the metanephros (Fig. 4.11). Lack of development of the ureteric bud will result in absence of permanent fetal kidneys, or renal agenesis. This anomaly is lethal if bilateral and is identified by a lack of amniotic fluid in the second trimester of pregnancy [24].

Highlights of Cardiac Development

A detailed review of the development of the human heart is beyond the scope of this chapter, due to the level of complexity of its formation. Highlights of cardiac development are reviewed in this section.

Early Cardiac Development

The cardiovascular system is the first organ system to begin functioning at 3–4 weeks of embryonic age. The cardiovascular system is primarily derived from splanchnic mesoderm, paraxial and

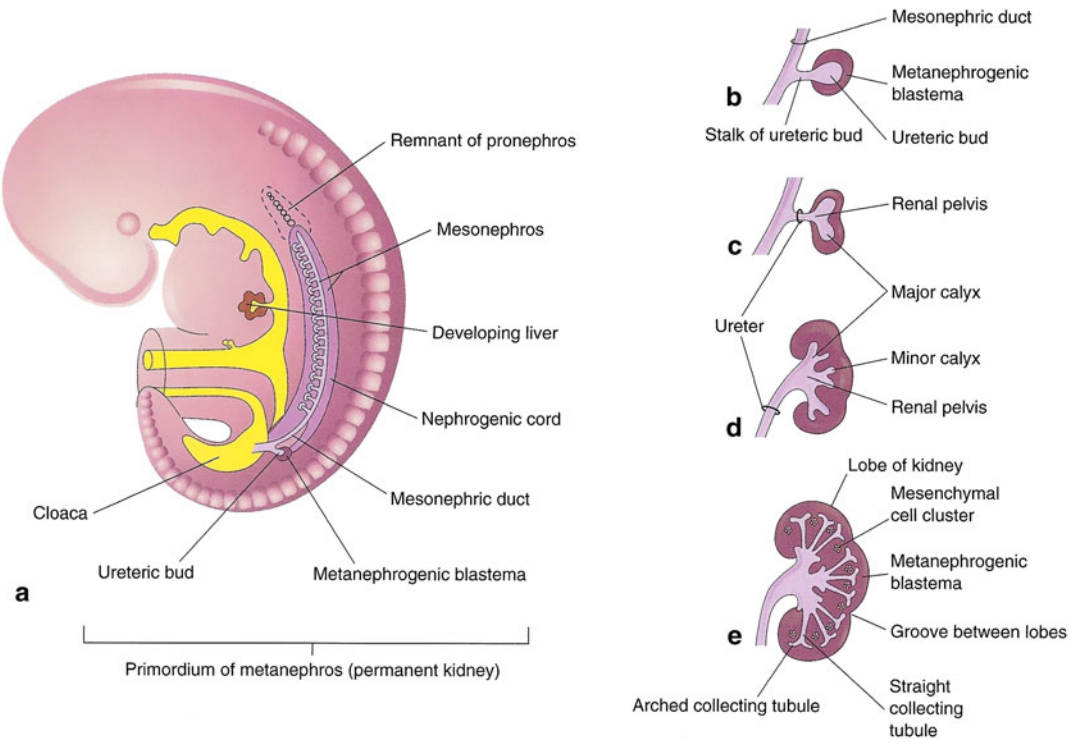

Fig. 4.11 Development of the permanent kidney. (**a**) Five-week human embryo showing the developing metanephros and ureteric bud. (**b**–**e**) Successive stages in the development of the ureteric bud. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

lateral mesoderm, and pharyngeal mesoderm, but also involves migration of neural crest cells [6]. Paired angiogenic cords, formed from the cardiogenic mesoderm, undergo fusion and canalization to form a simple tube, the initial cardiac structure. Blood begins flowing through the cardiac tube at approximately 4 weeks embryonic age. The outside of the single tube becomes the myocardium, and the inside of the tube becomes the endocardium. The epicardium (visceral pericardium) is derived from mesothelial cell proliferation from the external surface of the sinus venosus, which is a predecessor of the cardiac atria [25]. Folding of the head results in the heart location ventral to the foregut and caudal to the developing mouth.

After the formation of a single cardiac tube, partitioning of the heart begins at the end of the fourth embryonic week, continuing until the eighth to ninth week [6]. The developing heart begins to bend and constrict, resulting in the formation of five segmental primitive heart dilatations—the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and sinus venosus. The truncus arteriosus give rise to the precursors of the aorta and pulmonary trunk, the bulbous cordis and primitive ventricle give rise to the ventricles, and the primitive atrium and sinus venosus to the atria and coronary sinus. Dextral (right handed) cardiac looping is also initiated during this developmental period, believed to primarily occur during embryonic weeks 5–7 [25]. This looping results in a U-shaped loop, which has as its end result the normal axis of the heart (Fig. 4.12).

When the heart tube bends left, rather than right, the heart is displaced to the right and its great vessels are reversed, creating a mirror image of the

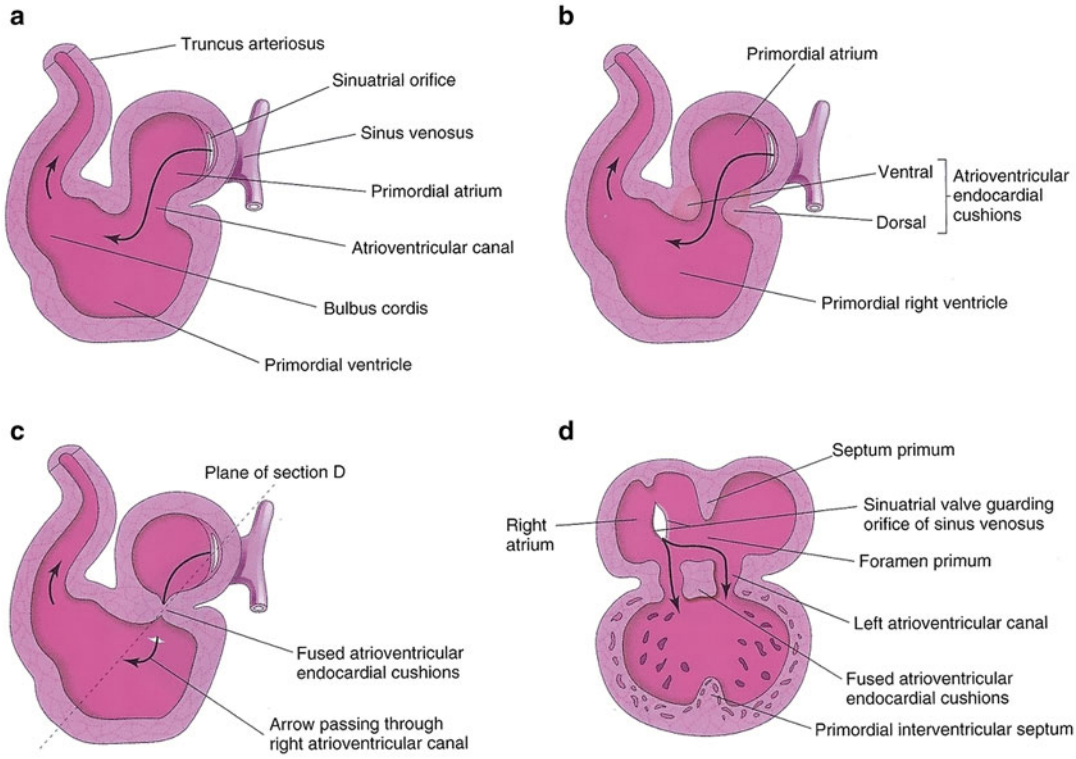

Fig. 4.12 Development of cardiac looping and atrioventricular (AV) septum development. (**a**, **b**) Sagittal sections of the heart at 4–5 embryonic weeks. (**c**) Fusion of the endocardial cushions to form the AV septum. (**d**) Coronal section of the heart at the place shown in (**c**). This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

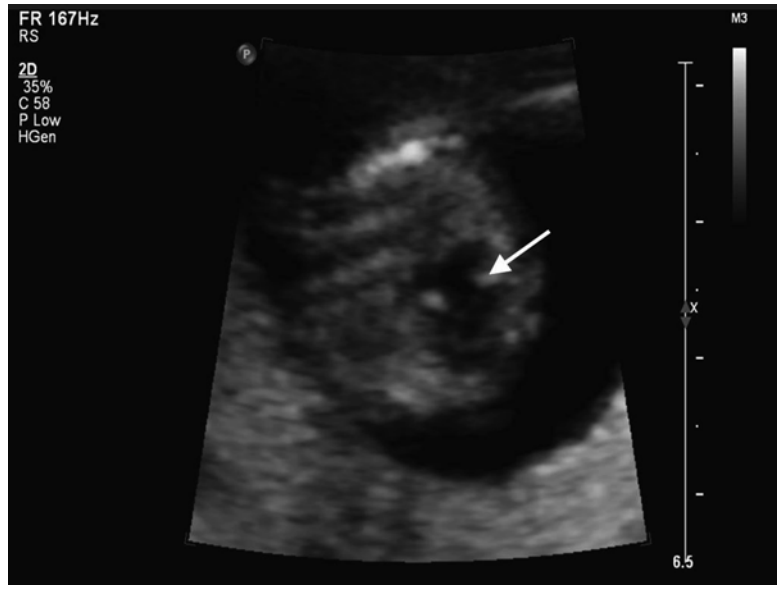

Fig. 4.13 Fetal persistent common atrioventricular (AV) canal at 13 weeks, a complication of abnormal endocardial cushion function or location. The *arrow* indicates the site of the absent AV septum, with a single shared AV valve for both sides of the heart. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

normal heart structure, called dextrocardia which can be associated in some cases with an increased risk of severe cardiac defects [26].

Cardiac Septae Formation and Valvular Development

Multiple separate cell migration and signaling pathway processes are involved in the complex development of appropriate cardiac septae:

Atrioventricular (AV) Septum

The AV endocardial cushions develop from a specialized extracellular matrix (cardiac jelly) within the walls of the AV-canal. These cushions move towards each other and eventually fuse to form the AV septum with separation of a common AV canal into left and right AV canals (see Fig. 4.12). The cushions then function as the AV valves until further differentiation occurs resulting in definitive valve structure. Inductive signals from the myocardium of the AV canal causes epithelial–mesenchymal transformation, which transforms the endocardial cushions and ultimately contributes to the development of the definitive AV valves and membranous septum of the heart [26].

Numerous cardiac anomalies are attributable to abnormal development of the endocardial cushions. Failure of cushion fusion is responsible for persistent common AV canal, in which there is no true septal division of the heart, and a single common atrioventricular valve in place of the tricuspid and mitral valves (Fig. 4.13). Inadequate amounts of endocardial cushion are also believed to be associated with abnormal development of the tricuspid valve, including abnormal location (Ebstein's anomaly) or congenital absence of the valve, the result of which can have devastating consequences for long term cardiac function [26].

Atrial Septum

Partitioning of the atria begins at the end of the fourth embryonic week [6]. The right and left atria are created by the fusion of two septae, the septum primum and septum secundum. The septum primum has an initial foramen, termed the foramen primum, and, subsequently, also develops the foramen secundum. As the septum secundum develops, an incomplete septation occurs resulting in the foramen ovale [27]. The inferior aspect of the septum primum becomes the flap (valve) of the foramen ovale, which should fuse anatomically shortly after birth. Excessive resorption of either the septum primum or septum secundum results in an atrial septal defect or persistent foramen ovale, which are several of the

most common congenital heart abnormalities. The female to male ratio for atrial septal defects is 3:1 [28].

Ventricular Septum

Partitioning of the ventricles also involves septation, accomplished by fusion of the muscular portion of the interventricular (IV) septum with the membranous area of the septum [6]. Until the seventh week of gestation a defect is noted in the IV septum between the free edge of the muscular portion and the lower component of the AV cushions. Closure of the defect typically occurs at the end of week seven, and involves fusion of the membranous portion of the IV septum with the muscular component [27]. Ventricular septal defects (VSDs) are the most common form of congenital cardiac abnormality, making up approximately 25 % of cases [29]. Typically the defect results from failure of the membranous portion of the septum to close, although other defects also occur. Many small VSDs close during embryonic and fetal development, although larger defects can result in cardiac dysfunction and require postnatal surgical management.

Aorticopulmonary (AP) Septum

Septation of the truncus arteriosus and bulbus cordis is critical to the normal cardiac development and outflow through the pulmonary trunk and the aorta. This occurs during the fifth embryonic week [6]. The AP septum is believed to be formed by mesenchyme derived from migrating neural crest cells, which invade the truncus arteriosus and bulbus cordis [27]. As the cells migrate, they develop in a spiral fashion, fusing to form the AP septum and separating the pulmonary and aortic outflow tracts (Fig. 4.14). Membranous tissue from the interventricular septum also fuses with the aorticopulmonary septum, resulting in a normal anatomic relationship where the pulmonary artery arises from the right ventricle and the aorta from the left ventricle (see Fig. 4.14). If neural crest cell migration does not proceed appropriately, the AP septum may not develop properly. This includes limited development of AP septum, with only one large vessel leaving the heart, called truncus arteriosus, as well as abnormal or absent spiraling of the septum causing transposition of each vessel from it appropriate ventricular outflow, called transposition of the great arteries. Unequal division of the truncus arteriosus is also believed to contribute to tetralogy of Fallot, in which pulmonary artery stenosis, ventricular septal defect, overriding aorta, and right ventricular hypertrophy are all identified [26].

Development of the Lymphatic System

Development of the lymphatic system begins and the end of the sixth embryonic week, *after* the cardiovascular system has developed [30]. It develops with a process similar to that for fetal blood vessels, with a series of small lymphatic tubes joining to form a lymphatic network (Fig. 4.15). Lymphatic drainage encompasses six primary lymph sacs, and many lymph nodes. Drainage occurs first from the cranial and caudad aspects of the embryo/fetus and then primarily into the right lymphatic duct. Abnormalities in lymphatic drainage, due to a blocked lymph sac or failure to establish appropriate lymphatic channels, may cause large swellings in the area of the fetal neck known as cystic hygromas (Fig. 4.16). The presence of a cystic hygroma is associated with and increased risk of fetal genetic abnormalities, cardiac malformations, and other fetal developmental problems [31, 32].

Summary

The human embryo and fetus undergoes remarkable development in the first trimester, from several cells to an embryo with clear organ structure and function. This formation is in large part affected by a complex system of embryonic cell signaling. Abnormalities in appropriate signaling function and cell migration, including those resulting from first-trimester teratogen exposure or genetic abnormalities, can have long-term complications for the developing fetus and newborn.

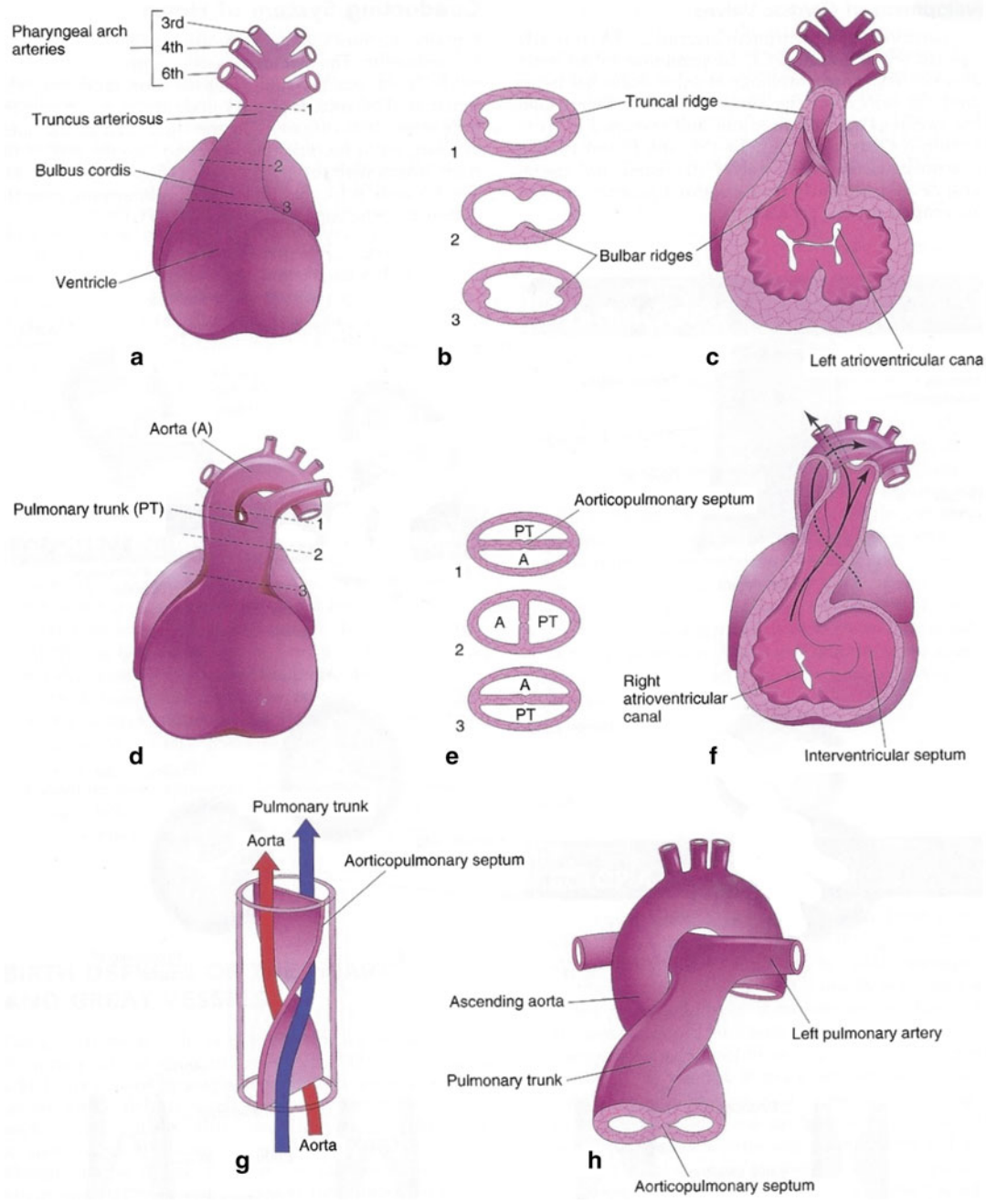

Fig. 4.14 Partitioning of the bulbus cordis and truncus arteriosus to form the great arteries. (**a**) Ventral view of the fetal heart at 5 weeks. *Broken lines* indicate the levels of the sections shown in (**b**). (**b**, **c**) Identification of the bulbar and truncal ridges forming the pulmonary and aortic outflow. (**d**–**f**) Ventral view of the fetal heart at 6 weeks after the aorticopulmonary (AP) septum is formed. (**g**) Spiral form of the AP septum, further illustrated in (**h**). This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

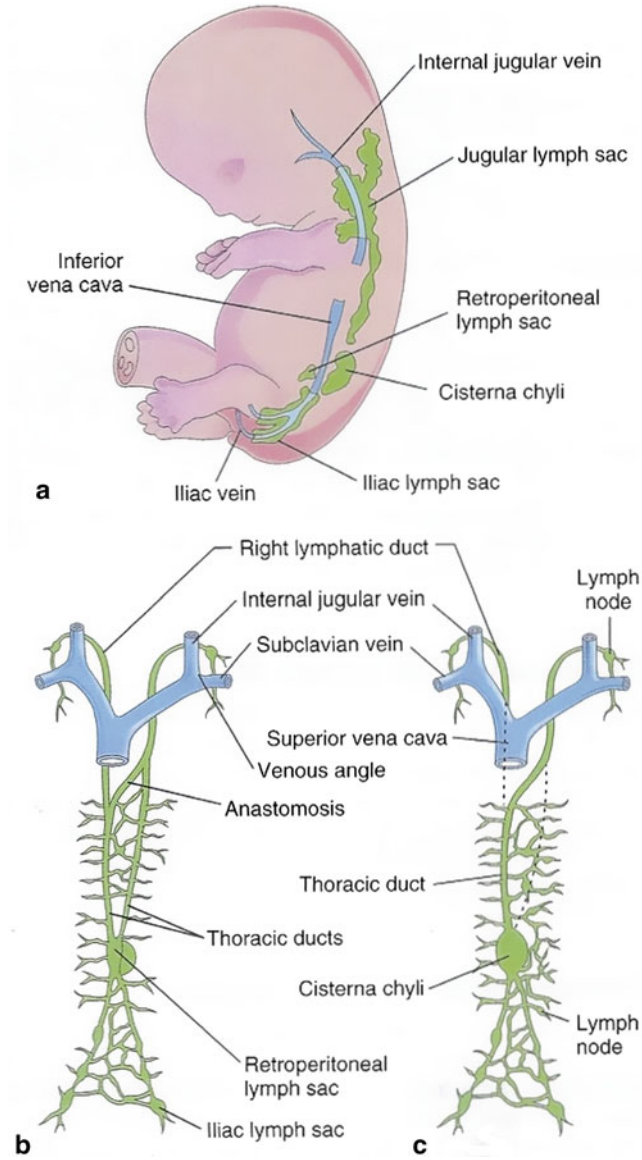

Fig. 4.15 Development of the lymphatic system. (**a**) Fetal embryo at 7 weeks showing primary lymph sacs. (**b**) Ventral view of lymphatic system at 9 weeks. (**c**) Formation of the thoracic and right lymphatic ducts later in gestation. This figure was published in The Developing Human: Clinically Oriented Embryology, 9th ed., Moore KL, Persaud TVN, Torchia MG, Copyright Elsevier 2013

Teaching Points

- Three percent of all pregnancies are complicated by a congenital anomaly.
- Signaling pathways are essential for normal morphogenesis
- The three germ layers are ectoderm, endoderm, and mesoderm; these are the building blocks for normal morphogenesis.
- The notochord is paramount to normal neurulation, axial orientation, and segmentation during early embryological development.
- Normal diaphragm development is dependent upon normal partitioning of the embryo and normal relationship of the septum transversum, dorsal mesentery of the esophagus, pleuroperitoneal membranes, and muscular ingrowth from the lateral body wall.
- Gastroschisis is believed to be the result of lack of fusion of the lateral folds of the embryo.

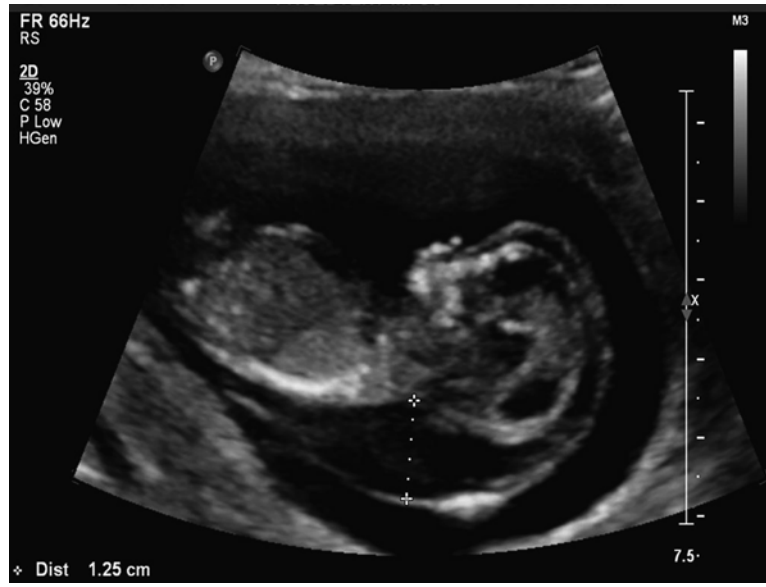

Fig. 4.16 Eleven-week ultrasound image of a fetus with longitudinal view of a cystic hygroma. Courtesy of Dr. Randall Kuhlmann, Division of Maternal Fetal Medicine, Medical College of Wisconsin, Milwaukee, WI

- Failure of endocardial cushion fusion results in various degrees of cardiac septal defects ranging from a membranous ventriculoseptal defect (VSD), to complete nonfusion and a common atrioventricular (AV) canal.

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Elements of Teratology

5

Eran Barzilay and Gideon Koren

Definition

A teratogen is defined as any agent that can produce an adverse fetal outcome, including congenital anomaly, miscarriage, intrauterine growth restriction, stillbirth, prematurity, or long-term developmental delay [1, 2]. Environmental factors that have a teratogenic potential include drugs, chemicals, infections, and physical factors (such as radiation).

Perception of Teratogenic Risk

Birth defects are not a rare phenomenon, and in most cases are not related to environmental agents [1]. A baseline risk for malformation of 1–3 % is a useful reference frame for evaluating the teratogenic risk of environmental exposures [3, 4]. Before thalidomide was recognized as a teratogen, the placenta was perceived to serve as a barrier that protected the developing embryo from any maternal exposure [2]. This perception may explain the fact that years had passed before thalidomide was recognized as a teratogen, despite a high rate of malformation and the characteristic pattern of malformations [5, 6]. The thalidomide disaster shifted the perception of risk to the other extreme, to a point that physicians and patients alike consider every drug as potentially harmful for the embryo [7]. Recent studies have shown that women exposed to agents not known to be teratogenic assigned themselves an unrealistically higher risk for major malformations and were more likely to terminate their pregnancy [7, 8]. Overestimation of teratogenic risk, aside from effecting decisions regarding pregnancy termination, may also prompt women to discontinue vital drug treatment and thereby endanger both their and their offspring's health.

An example for how erroneous perception of risk can affect medical practice is the withdrawal of bendectin from the market worldwide. Bendectin (a combination of vitamin B6 and doxylamine) was voluntarily removed from market by its manufacturer in 1983 due to multiple liability suites and the increase in insurance premiums. This happened despite the fact that an FDA investigation did not find an association between bendectin and birth defects. Following bendectin's withdrawal, admissions for excessive vomiting in pregnancy per thousand live births rose by 50 % in 1984 [9]. Another example for the possible detrimental effects of overestimation of teratogenic risk is the panic that followed the Chernobyl nuclear accident in 1986. A study from Greece estimated that 2500 otherwise

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wanted pregnancies were terminated due to perceived radiation risk, despite the fact that radiation levels in Athens were within normal levels [10]. Furthermore, according to the International Atomic Energy Agency, an estimated 100,000–200,000 wanted pregnancies were aborted in Western Europe because physicians advised patients that the radiation from Chernobyl posed a significant health risk to unborn children [11].

Teratogens

The baseline risk for major fetal malformations is estimated at 1–3 % [3, 4]. In most cases, the cause of the malformation is unknown. In 20–25 % the malformations are caused by genetic factors and in 8–11 % they are attributed to environmental factors [4]. Environmental factors that have been associated with congenital malformations include exposure to chemicals and drugs, maternal disease, infection, and exposure to radiation.

Drugs in Pregnancy

Prescription drugs are used in more than 50 % of pregnancies [12, 13]. Considering non-prescription drugs and drugs of abuse, the prevalence of exposure to drugs in pregnancy is probably much higher. Nevertheless, only a few drugs (Table 5.1) have been proven to be teratogenic in humans [2]. In most cases, the sensitive period for fetal development is in the first trimester. However, some drugs have been shown to affect the fetus in later pregnancy. For example, tetracycline exposure after 25 weeks might result in staining of teeth and possibly affect bone growth [14], third trimester exposure to nonsteroidal anti-inflammatory drugs has been associated with premature constriction of the ductus arteriosus and oligohydramnios [15, 16], and late exposure to ACE inhibitors has been associated with fetal and neonatal death, renal abnormalities, oligohydramnios, fetal skull ossification defects, and patent ductus arteriosus [17]. Moreover, because the fetal brain continues to develop throughout pregnancy, late effects of chemicals such as alcohol and tobacco smoke have been documented.

Alcohol

Ethanol (alcohol) consumption during pregnancy has been associated with a variety of birth anomalies, many of which can be demonstrated by ultrasound, as well as neurocognitive impairment.

Diagnosis of fetal alcohol spectrum disorder (FASD) requires:

1. Prenatal and/or postnatal growth restriction (weight, length, and/or head circumference below the 10th centile).
2. Central nervous system involvement (signs of neurological abnormality, developmental delay, behavioral effects or intellectual impairment).
3. Characteristic facial dysmorphology with at least two of these three signs:
   - Microcephaly
   - Microphthalmia and/or short palpebral fissures.
   - Poorly developed philtrum, thin upper lip, and/or flattening of maxillary area.

Structural malformations other than those of the face are sometime associated with FASD, including congenital heart defects, neural tube defects, renal abnormalities, cleft palate and minor malformations such as strabismus, unusual palmar creases, and poorly formed ears. Full expression of the fetal alcohol syndrome generally occurs with chronic ingestion of at least 2 g/kg/day of alcohol. A conservative estimation of malformation risk for women consuming more than 2 g/kg/day during the first trimester is a twofold to threefold increase in risk. It is possible that minor effects would be caused by smaller amounts of alcohol; however, a safe amount of alcohol consumption in pregnancy has not been determined [18–22].

Aminopterin

Aminopterin is a folic acid antagonist closely related to methotrexate. It has been used in the 1950s as an anticancer drug and to induce abortions.

Table 5.1 Drugs considered as teratogens and the main teratogenic effects that were associated with first-trimester exposure to these drugs

Drug	Teratogenic effects
Alcohol	Fetal alcohol syndrome, growth retardation, neurological abnormality, developmental delay, intellectual impairment, microcephaly, microphthalmia, short palpebral fissures, poorly developed philtrum, thin upper lip and/or flattening of maxillary area, congenital heart defects, neural tube defects, renal abnormalities, cleft palate.
Aminopterin	A "clover-leaf" skull, large head, swept-back hair, low-set ears, prominent eyes, wide nasal bridge, meningoencephalocele, anencephaly, brachycephaly, hydrocephaly, delayed calvarial ossification, craniosynostosis, ocular hypertelorism, micrognathia, oral clefts, limb anomalies, neural tube defects.
Benzodiazepines	Oral clefts (conflicting results).
Carbamazepine	Neural tube defects.
Carbon monoxide	Stillbirth, growth retardation, and severe neurological sequelae. Possibly also VSD and pulmonic stenosis.
Cocaine	Stillbirth, placental abruption, prematurity, low birth weight, microcephaly, intraventricular hemorrhage, and developmental difficulties. An association with urinary tract anomalies was suggested.
Corticosteroids	Cleft palate (conflicting results), fetal growth impairment.
Diethylstilbestrol	Abnormal urogenital tract development, increased risk of vaginal clear cell carcinoma.
Lithium	Ebstein's anomaly, other cardiac malformations.
Methotrexate	Intrauterine growth restriction, dysmorphic facial features, digital anomalies, limb, ear, skeletal, genital, skull, chin, central nervous system, spinal, cardiac, gastrointestinal defects, and oral clefts.
Methyl mercury, mercury sulfide	Fetal Minamata disease (microcephaly, seizures, ataxia, cognitive impairment and cerebral palsy).
Misoprostol	Moebius sequence (paralysis of the sixth and seventh cranial nerves).
Mycophenolate mofetil	Microtia, auditory canal atresia, cleft lip and palate, micrognathia, hypertelorism, ocular coloboma, short fingers, and hypoplasic nails.
PCB	Dark brown pigmentation of the skin and the mucous membrane, gingival hyperplasia, exophthalmic edematous eye, dentition at birth, abnormal calcification of the skull, rocker bottom feet, and low birth weight.
Penicillamine	Cutis laxa and inguinal hernia (conflicting results).
Phenobarbital	Cardiac defects and cleft palate.
Phenytoin	Broad nasal bridge, metopic ridging, microcephaly, cleft lip/palate, ptosis, variable degrees of hypoplasia of the distal phalanges.
Retinoids	Microtia/anotia, micrognathia, thymic, CNS and cardiac defects.
Thalidomide	Limb reduction defects, cardiac defects, facial hemangiomata, esophageal and duodenal atresia, renal defects, microtia, and anotia.
Valproic acid	Spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis.
Warfarin	Skeletal defects (nasal hypoplasia, stippled epiphysis), growth restriction, CNS damage, eye defects, and hearing loss.

Exposure to aminopterin in the first trimester has been associated with a "clover-leaf" skull with a large head, swept-back hair, low-set ears, prominent eyes and wide nasal bridge, as well as meningoencephalocele, anencephaly, brachycephaly, hydrocephaly, short stature, delayed calvarial ossification, craniosynostosis, ocular hypertelorism, micrognathia, oral clefts, limb anomalies, and neural tube defects. The critical period of exposure appears to be the sixth to eighth week of gestation [23–27]. Most of these malformations, such as anencephaly or micrognathia are recognizable by ultrasound, often in early gestation.

Benzodiazepines

Based on meta-analysis of case control studies, benzodiazepines may increase the risk for oral cleft; however, data in the literature showed conflicting results concerning this matter. Pooled data

from cohort studies showed no association between fetal exposure to benzodiazepines and the risk of major malformations or oral cleft. On the basis of pooled data from case–control studies, however, there was a significant increased risk for major malformations or oral cleft alone. The absolute increase in risk for oral clefts, if it exists, appears to be very low (incidence of oral clefts in the general population is about 1 in 1000) [28, 29]. Oral clefts should be recognized with ultrasound examination of the fetal face.

Carbamazepine

Exposure to carbamazepine monotherapy in utero increases the risk of neural tube defect (NTD) to a higher rate than the general population but less than that associated with valproic acid. The risk of NTD has been estimated to increase from a baseline of about 0.1 % to a level of 0.2–1 % [30–35]. Fetal spine examination is part of any routine ultrasound anatomy study.

Carbon Monoxide Poisoning

Mild carbon monoxide poisoning was not associated with increased fetal risk, but adverse fetal outcomes were noted with severe maternal toxicity, including a high risk of stillbirth, growth restriction, and severe neurological sequelae (mental retardation, seizures, spasticity). An association with ventricular septal defect (VSD) and pulmonic stenosis was also suggested. The relative risk for birth defects in cases of carbon monoxide poisoning is unknown. Most adverse effects were observed when toxicity was severe enough to cause maternal symptoms [36–38].

Cocaine

Studies on the effect of cocaine exposure in pregnancy frequently suffer from methodological drawbacks that make the results difficult to interpret. Most women who abuse cocaine are polydrug abusers, use alcohol, smoke, and have other risk factors for poor pregnancy outcome including poor nutrition, high gravidity, and lack of prenatal care. Cocaine use in pregnancy has been associated with an increased risk for stillbirth, placental abruption, prematurity, lower birth weight, and microcephaly compared to non-exposed infants. Associations with intraventricular hemorrhage, developmental difficulties and sudden infant death syndrome (SIDS) have also been suggested. There is disagreement on whether cocaine use increases the risk of structural malformations, although some studies show an increase in urinary tract anomalies [39–44].

Corticosteroids

Corticosteroids have been consistently shown to produce cleft palate in animals. Human studies have shown conflicting results. A possible association with oral clefts cannot be excluded. Glucocorticoids are associated with fetal growth impairment. The absolute increase in risk for oral clefts, if it exists, appears to be low (baseline 0.1 %) [45–51]. Oral clefts can be observed during examination of the fetal face.

Diethylstilbestrol

Diethylstilbestrol (DES) has been associated with abnormal urogenital tract development and an increased risk of vaginal clear cell carcinoma. Vaginal adenosis was reported in up to 50 % of offspring and the incidence of preterm deliveries was reported as 11–39 % [52, 53].

Lithium

Lithium use has been associated with cardiac malformations in general and specifically with Ebstein's anomaly. Early information regarding teratogenic risk of lithium was derived from retrospective reports with a high risk of bias. More recent studies indicate that the risk is much lower. Risk for Ebstein's anomaly after first-trimester exposure has been estimated as 0.05–0.1 % [54–56]. This cardiac anomaly has specific components (displacement of the septal and posterior leaflets of the tricuspid valve towards the apex of the right ventricle of the heart, resulting in the typical appearance with a large right atrium and a small right ventricle) that can be observed in a simple four-chamber view of the heart (see Chap. 11).

Methotrexate

Methotrexate is a folic acid antagonist closely related to aminopterin. Several reports on exposure to single high-dose methotrexate, in cases of failed termination of pregnancy or misdiagnosis of

ectopic pregnancy, have demonstrated a variety of anomalies. The anomalies noted on prenatal ultrasonography and/or at birth included intrauterine growth restriction, dysmorphic facial features, digital anomalies, limb, ear, skeletal, genital, skull, chin, central nervous system, spinal, cardiac, gastrointestinal defects, and oral clefts. A recent prospective observational study on pregnancy outcome in women taking methotrexate (up to 30 mg/week) for rheumatic disease demonstrated that among women exposed to methotrexate post conception (188) 42.5 % had spontaneous abortions and the risk of major birth defects was elevated (6.6 %, odds ratio 3.1, 95 % CI 1.03–9.5). The observed malformations included gastroschisis, scoliosis, CCAM, cardiac malformation, renal malformations, limb defects, holoprosencephaly, and megabladder. Women planning a pregnancy after MTX therapy should be counseled to use contraception and folate supplementation during therapy and for a period of 3 months after stopping the drug [23, 25, 26, 57–63].

Methyl Mercury, Mercury Sulfide

Exposure to high levels of organic mercury in utero may cause fetal Minamata Disease, manifested by microcephaly, seizures, ataxia, cognitive impairment, and cerebral palsy. Relative risk has not been established; however, 13/220 babies born in Minamata at the time of contamination suffered from severe disease [64–66].

Misoprostol

Exposure to misoprostol is associated with Moebius sequence (paralysis of the sixth and seventh cranial nerves). Association with other malformations, such as limb reduction defects, abnormalities of frontal and temporal bones in the skull, has been suggested but not confirmed. Odds ratio for Moebius sequence was reported to be 25.32 (95 % CI 11.11–57.66). However, the true risk is less than 1–2 %. Odds ratio for limb reduction was estimated to be 11.86 (95 % CI 4.86–28.9).

Mycophenolate Mofetil

Exposure to mycophenolate mofetil has been associated with birth defects including microtia, auditory canal atresia, cleft lip and palate, micrognathia, hypertelorism, ocular coloboma, short fingers, and hypoplasic nails [67]. A higher incidence of structural malformations was seen with mycophenolate mofetil exposures during pregnancy compared to the overall kidney transplant recipient population [68]. The risk for birth defect following first-trimester exposure to mycophenolate mofetil has been reported as 26 % [68, 69].

Polychlorinated Biphenyls

Exposure to high levels of polychlorinated biphenyls (PCB) has been reported in cases of accidental human exposure to rice oil contaminated with PCBs. Exposure to high levels of PCBs is associated with dark brown pigmentation of the skin and the mucous membrane, gingival hyperplasia, exophthalmic edematous eye, dentition at birth, abnormal calcification of the skull, rocker bottom feet, and low birth weight [70].

Penicillamine

Data regarding exposure to penicillamine are conflicting. However, there may be an association with cutis laxa and inguinal hernia. Hypothyroidism was also suggested to be associated with penicillamine exposure [71, 72].

Phenobarbital

Phenobarbital use may be associated with cardiac defects and cleft palates. According to some reports, there is 6–20 % risk for malformation. Other reports did not find an increase in risk. A study of 250 cases of monotherapy exposure reported that the risk for major malformation was not greater than other anticonvulsant monotherapies [73–76].

Phenytoin

A pattern of malformations has been associated with in utero phenytoin exposure, referred to as fetal hydantoin syndrome. The pattern of malformation includes craniofacial abnormalities such as broad nasal bridge, metopic ridging, microcephaly, cleft lip/palate, and ptosis, as well as variable degrees of hypoplasia and ossification of the distal phalanges. The risk of teratogenicity with phenytoin exposure in the first trimester was defined as 10 %. However, subsequent

reports have found a lower risk for malformations, and the relative risk was estimated to be about 2–3 [31, 77, 78].

Systemic Retinoids

Use of systemic retinoids such as isotretinoin in pregnancy is associated with an increased risk for malformations. The most common anomalies include microtia/anotia, micrognathia, thymic hypoplasia, aplasia or ectopic location, CNS and cardiac defects (VSD, tetralogy of Fallot, and transposition of the great vessels), most of which are recognizable by ultrasound. Due to a relatively long half-life, a waiting period of at least 1 month is recommended by some authors, while others recommended a 3-months waiting period. The risk for malformations with exposure to isotretinoin after conception was estimated to be 35 %. Forty-three percent of exposed to isotretinoin were found to have a subnormal IQ (<85) [79, 80].

Thalidomide

Use of thalidomide during the first trimester is associated with limb reduction defects, cardiac defects, facial hemangiomata, esophageal and duodenal atresia, renal defects, microtia, and anotia. The risk was estimated to be 20–30 % when exposure occurs between gestational weeks 5 and 7 [5, 6].

Valproic Acid

Use of valproic acid in pregnancy is associated with an increased risk for major malformation. The specific malformations found in association with valproic acid are spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis. The highest relative risk compared with no use of antiepileptic drugs was for spina bifida (relative risk of 12). Relative risk for the other conditions was 2–7. Exposure to monotherapy with valproic acid was associated with a relative risk of 2.6 for major malformation (95 % CI 2.11–3.17) when compared to monotherapy with other antiepileptic drugs, 3.2 (95 % CI 2.2–4.6) when compared to untreated epileptic patients and 3.77 (95 % CI 2.18–6.52) when compared to healthy controls. The risk for malformations appears to be dose dependent. Absolute risk for spina bifida is usually quoted as 1–2 %. A more recent study had an absolute risk of 0.6 % for spina bifida [81–84]. Detailed ultrasound anatomy survey is indicated in mothers who received this medication.

Warfarin

Exposure to warfarin between 6 and 12 weeks of gestation has been associated with skeletal defects (such as nasal hypoplasia and stippled epiphysis), intrauterine growth restriction, CNS damage, eye defects, and hearing loss. Exposure after the first trimester might increase the risk of CNS defects, perhaps due to microhemorrhages. The absolute risk is not clear. One review sited a 6.4 % risk for congenital anomalies [85–88].

Infections

Maternal infections during pregnancy are very common and in most cases do not interfere with fetal development. However, there are some pathogens, including bacteria, viruses, and parasites that may lead to fetal death, birth defects, and long-term sequelae.

Cytomegalovirus

Cytomegalovirus (CMV) is one of the most common causes of intrauterine infection [89]. CMV can pass from mother to fetus through the placenta or during a vaginal delivery. Fetal CMV infection is mostly associated with maternal primary CMV infection during pregnancy. However, fetal CMV infection has been reported in recurrent infection as well, albeit with a much lower risk [90, 91]. Transmission of the virus from the mother to the fetus occurs more frequently in more advanced gestational age, but the risk for permanent sequelae is higher if transmission to the fetus occurred in the first trimester [92]. The estimated risk of transmission in cases of maternal primary CMV infection is 30–40 % [93]. Birth abnormalities, including microcephaly, ventriculomegaly, intracranial calcifications, jaundice, and deafness, are apparent in about 10 % of infants born with congenital CMV infection.

The cranial ultrasound findings have been extensively described in the literature. Most of the symptomatic infants will suffer from sequelae such as sensorineural hearing loss and learning disabilities, and the most severe cases will have a high mortality rate [89, 90]. The asymptomatic cases (about 90 % of children born with congenital CMV) may develop progressive sensorineural hearing loss at a frequency of 13–15 %. In cases of recurrent infection, only 0.2–1 % of infants will be infected [93]. Of these, less than 1 % will show symptoms at birth, and 10 % of the asymptomatic newborns may experience hearing loss later in life.

Parvovirus B19

Approximately 50 % of pregnant women are believed to be immune to B19. In cases of maternal infection during pregnancy, vertical transmission has been reported as 25–33 % [94, 95]. Parvovirus does not seem to increase the risk for birth defects. However, fetal infection has been associated with fetal hydrops and death, mostly with infection before 20 weeks. The estimated risk for fetal death, if maternal infection occurs before 20 weeks gestation, is 1–9 %. If maternal infection occurs after 20 weeks gestation, the risk of hydrops is estimated to be 1 % [96].

Rubella

Due to widespread childhood vaccination, rubella infections rarely occur nowadays. Rubella in pregnancy may infect the fetus, producing congenital malformations, miscarriage or fetal death [97, 98]. The main defects associated with congenital rubella infection are cataracts, glaucoma, heart defects, deafness, pigmentary retinopathy, microcephaly, developmental delay, and radiolucent bone disease. Infants with congenital rubella syndrome usually present with more than one of these signs or symptoms. More than half of the patients will have three or more defects. Hearing impairment is the most frequently reported clinical manifestation, and is most likely to present as a single defect [97–99]. Almost all birth defects caused by rubella are associated with infections in the first 16 weeks. However, later infection has been associated with growth restriction and cases of deafness and pulmonary artery stenosis have been reported [99]. Congenital rubella survivors have an increased risk for type I diabetes, thyroid dysfunction, and progressive rubella panencephalitis [99, 100]. In cases of maternal rubella infection during the first trimester, the risk of malformation may be as high as 90 %.

Toxoplasma Gondii

The overall maternal-fetal transmission rate in cases of maternal toxoplasmosis in pregnancy was reported to be about 30 %. The risk of transmission to the fetus increases with gestational age from 6 % at 13 weeks to 72 % at 36 weeks. However, fetuses infected in early pregnancy were much more likely to show clinical signs of infection [101]. Symptoms of congenital toxoplasmosis present at birth can include a maculopapular rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, jaundice, and/or thrombocytopenia. However, 70–90 % of infants with congenital infection are asymptomatic at birth and sequelae can develop months or even years later. Up to 85 % will develop chorioretinitis, 20–75 % will have some form of developmental delay and 10–30 % will have moderate hearing loss [102–104].

Treponema Pallidum

Treponema Pallidum can infect the fetus at 14 weeks gestation, and possibly earlier. The risk for fetal infection increases with gestational age. In cases of fetal infection 40–50 % of the fetuses will die in utero while 30–40 % will be born with signs of congenital syphilis [105]. Signs of congenital syphilis may include hydrops fetalis, an unexpectedly large placenta, intractable diaper rash, jaundice, hepatosplenomegaly and anemia. Hepatosplenomegaly has been reported in almost 90 % of all such babies, and jaundice in 33 % of these neonates. The jaundice may be caused by syphilitic hepatitis or by hemolytic components of the disease [106]. Generalized lymphadenopathy usually occurs in association with hepatosplenomegaly and has been described in 50 % of the patients. In one study of nine patients with congenital syphilis, eight had evidence of anemia, four had evidence of thrombocytopenia, and six had jaundice [107].

Varicella

Varicella zoster virus infection (chickenpox) is a very common childhood infection which is usually mild in children, but can be more serious in newborn babies and adults. Pregnant women in the third trimester are at higher risk for more severe disease including varicella pneumonia [108]. Fetal infection has been associated with a syndrome of congenital anomalies. Features of the congenital varicella embryopathy include skin lesions and hypopigmentation, eye defects (cataracts, microphthalmia, chorioretinitis), neurologic abnormalities (microcephaly, mental retardation, cortical atrophy), limb and muscle hypoplasia, gastrointestinal reflux, urinary tract malformations, intrauterine growth restriction, developmental delay, and cardiovascular malformations [108]. Based on the case reports and larger studies it is now believed that the sensitive period for fetal effects is from 0 to 20 weeks of pregnancy, although there are case reports of clinical embryopathy after maternal infection at up to 28 weeks of gestation [109]. The risk for congenital varicella embryopathy in cases of maternal infection before 20 weeks gestation ranges from less than 1 % [109–111] to 3 % [112]. Maternal infection in the third trimester does not cause malformation; however, it can cause severe neonatal varicella and herpes zoster in the infant. There seems to be an increase in neonatal varicella severity when maternal rash appears 7 days before to 7 days after delivery, with most severe cases when rash appeared in the mother from 4 days before and up to 2 days after delivery [109].

Physical Factors

Ionizing Radiation

High levels of ionizing radiation have been shown to interfere with fetal development. Exposure to high levels of ionizing radiation has been associated with fetal death, growth restriction, microcephaly, organ aplasia and hypoplasia, oral clefts, cataracts, CNS malformations, and mental retardation [113–116]. In very early pregnancy, especially in the preimplantation period of the pregnancy, the embryo is mainly sensitive to the lethal effect of radiation [117]. During early organogenesis the embryo is also sensitive to the growth-restricting and teratogenic effects of radiation [118], while during the early fetal period, the effects are mainly on fetal growth and CNS development [119]. Exposure to ionizing radiation is very common and is frequently associated with medical procedures [120]. While radiation exposure in pregnancy is a cause for much anxiety, in most cases, exposure to ionizing radiation in various diagnostic imaging tests is much below the 5 rad threshold, which is the commonly accepted safe level of exposure in pregnancy.

Non-ionizing Radiation

Exposure to electromagnetic fields is very common. Exposure to non-ionizing radiation can theoretically pose a risk of thermal damage, especially to the eyes (because they cannot dissipate heat efficiently). The nonthermal effects have not been clearly demonstrated. However, there is currently no indication that this type of radiation can produce malignancy or mutations [121].

Ultrasound Waves

Studies on diagnostic ultrasound have not found any measurable effect on the fetus [122–125], and the fetal anomaly rate was comparable to the general population [126]. No effect was demonstrated on Apgar scores, gestational age, head circumference, birth weight, length, congenital abnormalities, neonatal infection, and congenital infection. At 7–12 years of age, there was no effect on hearing, visual acuity and color vision, cognitive function or behavior [127, 128]. Furthermore, diagnostic ultrasound was not found to increase the risk of childhood malignancy up to 6 years [129]. On the other hand, therapeutic ultrasound involves higher intensity and may produce deep tissue heating. Studies in rats showed a lower weight but no fetal damage [130]. However, because of the potential of hyperthermia to induce birth defects it is advised to avoid therapeutic ultrasound during pregnancy [121] (see Chap. 1).

Summary

Only a handful of drugs and other exposures have proven to be teratogenic in human. However, women tend to overestimate teratogenic risk. In many cases, overestimation of risk may cause women to discontinue essential medications or alternatively to terminate wanted pregnancies. Evidence-based teratogen risk counseling is therefore needed to promote evidence-based rather than fear-based decision making.

Teaching Points

- In every pregnancy, regardless of maternal diseases or environmental exposures, there is a 1–3 % risk of major malformation.
- Only a handful of drugs and other environmental exposures have been proven to be teratogenic.
- For most teratogens there is a typical pattern of malformations, commonly recognizable by ultrasound.
- Women tend to overestimate teratogenic risk and may act according to this misperception by discontinuing essential medications or terminating a wanted pregnancy.
- Evidence-based teratogen risk counseling is needed to promote evidence-based rather than fear-based decision making.

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First-Trimester Ultrasound: Guidelines

6

Jude P. Crino and Robert M. Ehsanipoor

Guidelines and recommendations for the performance of first-trimester ultrasound have been developed and published by several societies and organizations, including the American College of Obstetricians and Gynecologists (ACOG), American College of Radiology (ACR), American Institute of Ultrasound in Medicine (AIUM), Australasian Society for Ultrasound in Medicine (ASUM), Hong Kong College of Obstetricians and Gynaecologists (HKCOG), International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), National Institute of Child Health and Human Development (NICHD), Society for Maternal-Fetal Medicine (SMFM), Society of Obstetricians and Gynaecologists of Canada (SOGC), Society for Reproductive Endocrinology and Infertility (SREI), and Society of Radiologists in Ultrasound (SRU) [1–10]. These guidelines and recommendations have been published in a variety of printed and online formats. Several of these organizations have published collaborative guidelines. This chapter summarizes the key components of the various first-trimester ultrasound guidelines and recommendations. All concepts are not covered in each guideline, and pertinent differences between the published guidelines are described.

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Equipment

Most guidelines state that studies should be conducted with real-time scanners, using a transabdominal or transvaginal approach. The ISUOG guidelines specify minimum capabilities of the equipment, including real-time, gray-scale, two-dimensional ultrasound, transabdominal and transvaginal ultrasound transducers, adjustable acoustic power output controls with output display standards, freeze frame and zoom capabilities, electronic calipers, capacity to print/store images, and regular maintenance and servicing [5]. Fetal exposure times should be minimized, using the shortest scan times and lowest possible power output needed to obtain diagnostic information. Doppler examination should only be used in the first trimester if clinically indicated [11, 12].

Indications

The most comprehensive list of indications for first-trimester ultrasound is published in the collaborative ACOG/ACR/AIUM/SRU guideline [1]. These indications are listed in Table 6.1. In asymptomatic women with a known last

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Table 6.1 Indications for first-trimester ultrasound examination [1]

Confirmation of the presence of an intrauterine pregnancy
Evaluation of a suspected ectopic pregnancy
Defining the cause of vaginal bleeding
Evaluation of pelvic pain
Estimation of gestational (menstrual) age
Diagnosis or evaluation of multiple gestations
Confirmation of cardiac activity
Imaging as an adjunct to chorionic villus sampling, embryo transfer, and localization and removal of an intrauterine device
Assessing for certain fetal anomalies, such as anencephaly, in high-risk patients
Evaluation of maternal pelvic masses and/or uterine abnormalities
Measuring the nuchal translucency (NT) when part of a screening program for fetal aneuploidy
Evaluation of a suspected hydatidiform mole

menstrual period (LMP), it remains controversial whether or not to offer routine first-trimester ultrasound to confirm an ongoing early pregnancy.

Timing of First-Trimester Ultrasound

The first trimester is defined as a gestational age of up to 13 6/7 menstrual weeks of gestation. The embryonic period encompasses the first 10 menstrual weeks, and some guidelines state that the term "embryo" should be used before 10 weeks and "fetus" thereafter. For some indications and purposes, the timing of the ultrasound requires more specific limits. For example, aneuploidy screening and evaluation of fetal gross anatomy should be performed between 11 and 13 6/7 weeks of gestation, and pregnancy dating is more accurate earlier in the first trimester [5, 13].

Content of the Examination

Components of a standard first-trimester examination are assessment of pregnancy location, fetal number, fetal viability, measurements, determination of gestational age, and assessment of other intrauterine and extrauterine structures. Assessment of fetal anatomy and fetal aneuploidy assessment may be appropriate for some patients.

Pregnancy Location

The location of the pregnancy should be determined and documented. A definitive diagnosis of intrauterine pregnancy can be made when an intrauterine gestational sac containing a yolk sac or embryo/fetus with cardiac activity is visualized. Follow-up sonography and/or serial determination of maternal serum human chorionic gonadotropin levels are appropriate in pregnancies of undetermined location (see also Chap. 10) [1].

Fetal Number

Although the visualization of multiple sacs early in the first trimester is suspicious, the diagnosis of a multiple pregnancy requires visualization of multiple embryos/fetuses. The first trimester is the optimum time to determine chorionicity and amnionicity, which are critical for management of multi-fetal pregnancies. The presence of separate sacs, the thickness of the intervening membrane, and the shape of its junction with the placenta should be assessed [2] (Fig. 6.1). Early in the first trimester, an intervening amnion may not be visible in diamniotic–monochorionic twins [2]. Amnionicity and chorionicity should be stated in the ultrasound report.

Assessment of Viability

Although the term "viability" implies the ability to live independently outside of the uterus, from an ultrasound perspective, the term is used to describe the presence of an embryo with cardiac activity at the time of the examination [5]. An alternative definition, proposed by the SRU, is a pregnancy that can potentially result in a live-born baby. Updated diagnostic criteria for pregnancy viability have recently been published by the SRU due to occurrences of women diagnosed with miscarriage or ectopic pregnancy that resulted in damaging interventions to potentially normal pregnancies [10]. Findings diagnostic of pregnancy failure using transvaginal ultrasound include a crown-rump length (CRL) of ≥7 mm and no heartbeat, mean sac diameter (MSD) of

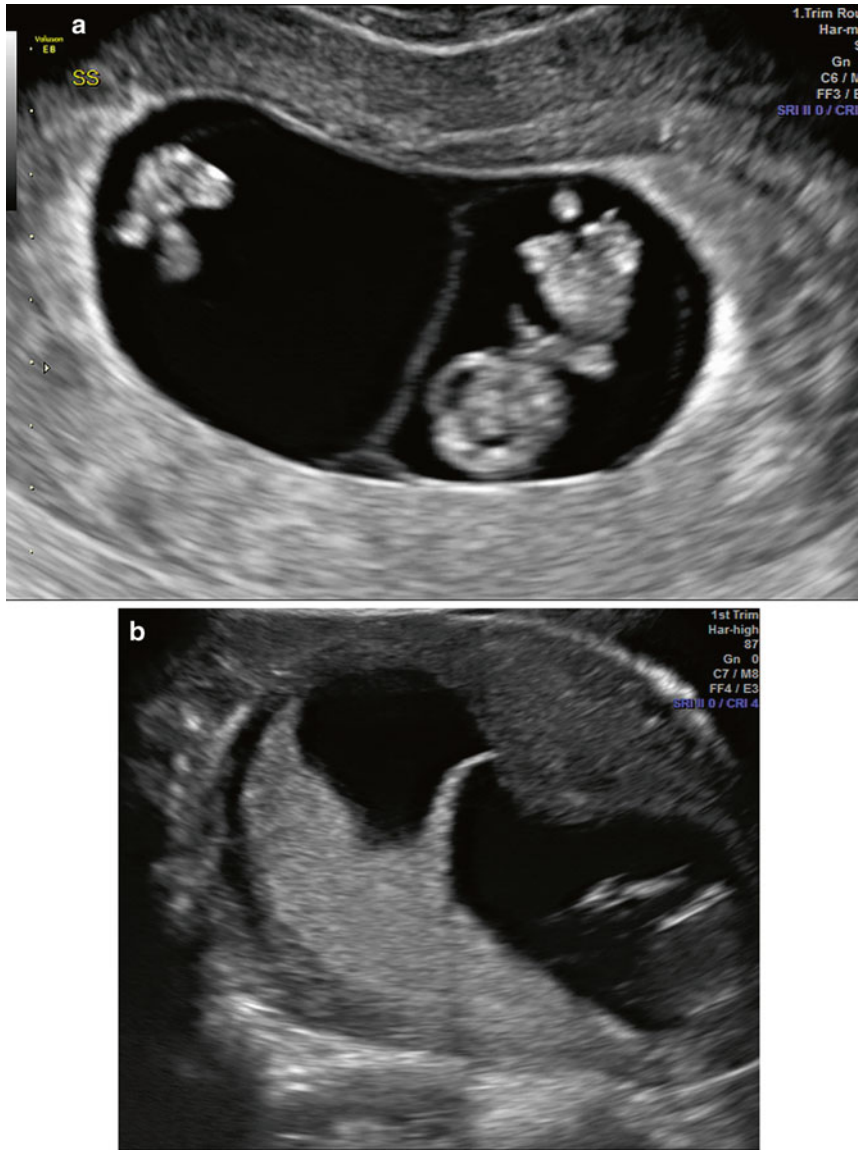

Fig. 6.1 (**a**) Monochorionic twin pregnancy at 9 weeks of gestation. Note the thin intervening membrane with no placental tissue. (**b**) Dichorionic twin pregnancy at 12 weeks of gestation. Note the thick intervening membrane with placental tissue ("twin peak" sign)

≥25 mm and no embryo, absence of an embryo with a heartbeat ≥2 weeks after a scan that showed a gestational sac without a yolk sac, and absence of an embryo with a heartbeat ≥11 days after a scan that showed a gestational sac with a yolk sac. Findings suspicious for, but not diagnostic of, pregnancy failure using transvaginal ultrasound include a CRL of <7 mm and no heartbeat, MSD of 16–24 mm and no embryo, absence of an embryo with a heartbeat 7–13 days after a scan that showed a gestational sac without a yolk sac, absence of an embryo with a heartbeat 7–10 days after a scan that showed a gestational sac with a yolk sac, absence of an embryo ≥6weeks after LMP, empty amnion (amnion seen adjacent to yolk sac, with no visible embryo), enlarged yolk sac (>7 mm), and a small gestational sac in relation to the size of the

Table 6.2 Terminology used early in the first trimester of pregnancy[a]

Terminology	Comments
Viable	A pregnancy is viable if it can potentially result in a liveborn baby
Nonviable	A pregnancy is nonviable if it cannot possibly result in a liveborn baby. Ectopic pregnancies and failed intrauterine pregnancies are nonviable
Intrauterine pregnancy of uncertain viability	A woman is considered to have an intrauterine pregnancy of uncertain viability if transvaginal ultrasonography shows an intrauterine gestational sac with no embryonic heartbeat (and no findings of definite pregnancy failure)
Pregnancy of unknown location	A woman is considered to have a pregnancy of unknown location if she has a positive urine or serum pregnancy test and no intrauterine or ectopic pregnancy is seen on transvaginal ultrasonography

[a]Reprinted with permission from Doubilet PM, Benson CB, Bourne T, Blaivas M. Diagnostic criteria for nonviable pregnancy early in the first trimester. Ultrasound Quarterly 2014 Jan; 30(1)

embryo (<5 mm difference between MSD and CRL). This group has also proposed that specific terminology be used, as summarized in Table 6.2.

Early Pregnancy Measurements

The MSD and CRL should routinely be measured and reported. The MSD is the average of three orthogonal measurements of the fluid filled space within the gestational sac (Fig. 6.2). The CRL is the maximum length of the entire embryo or fetus measured as a straight line in a true midsagittal plane (Fig. 6.3). Later in the first trimester, care should be taken to ensure that the fetus is not flexed by looking for the presence of fluid between the fetal chin and chest (Fig. 6.4). The ISUOG guidelines state that the biparietal diameter (BPD) and head circumference (HC) may also be measured after 10 weeks of gestation [5].

Assessment of Gestational Age

By convention, the term "gestational age" refers to menstrual age and represents post-conception (post fertilization) age plus 14 days [5]. First-trimester measurement of the CRL is the most accurate method to establish or confirm gestational age, with an accuracy of ±5–7 days. Gestational age determination by CRL is more accurate than MSD; therefore, MSD should not be used to determine the expected due date. A recent collaborative ACOG/AIUM/SMFM committee opinion on the method for estimating the due date specifies guidelines for re-dating based on ultrasonography [13]. Discrepancies between ultrasound dating and LMP dating that support re-dating based on CRL measurement are more than 5 days at ≤8 6/7 weeks, and more than 7 days from 9 0/7 weeks to 13 6/7 weeks.

Assessment of Fetal Anatomy

Published guidelines differ significantly on the issue of fetal anatomy assessment in the first trimester. The collaborative ACOG/ACR/AIUM/SRU guideline states only that embryonic/fetal anatomy appropriate for the first trimester should be assessed [1]. The ISUOG guidelines, on the other hand, suggest a more specific and detailed anatomical assessment between 11 and 13 6/7 weeks, including the head, neck, face, spine, chest, heart, abdomen, abdominal wall, extremities, placenta, and umbilical cord, but state that such an assessment should only be performed if requested [5]. The ISUOG suggested anatomical assessment is summarized in Table 6.3.

Fetal Aneuploidy Assessment

The guidelines state that, when requested for patients desiring to assess their individual risk of fetal aneuploidy, measurement of the nuchal translucency (NT) combined with serum biochemistry may be performed. NT implementation

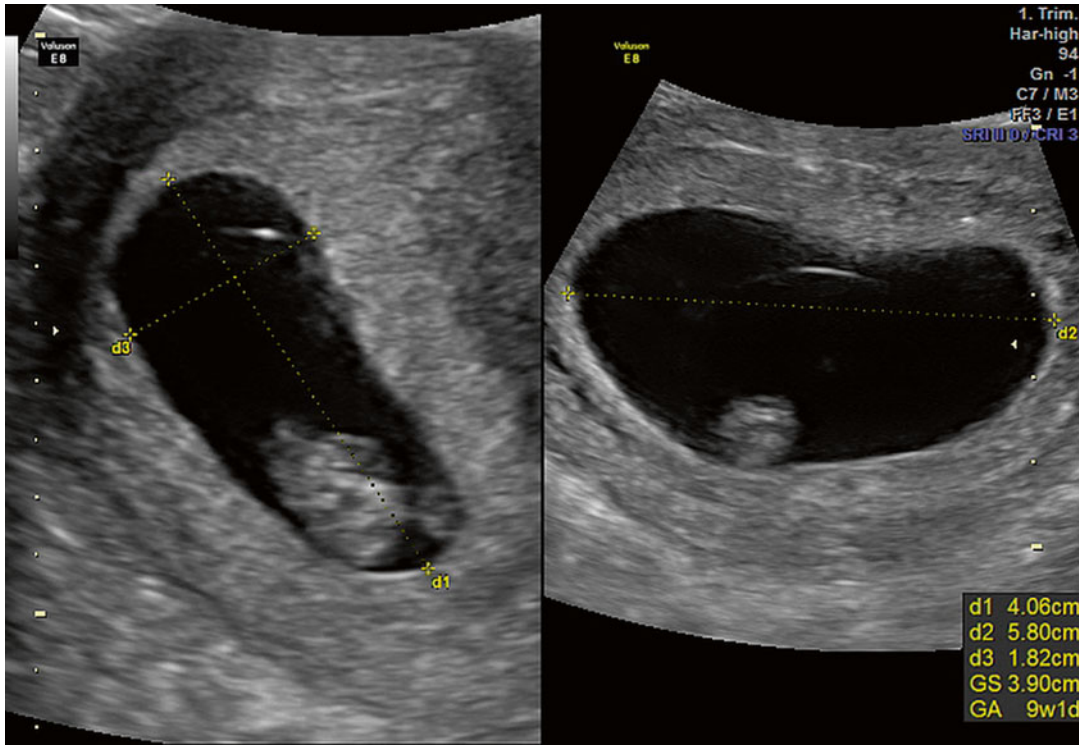

Fig. 6.2 Measurement of the mean gestational sac diameter in three orthogonal planes at 9 weeks of gestation

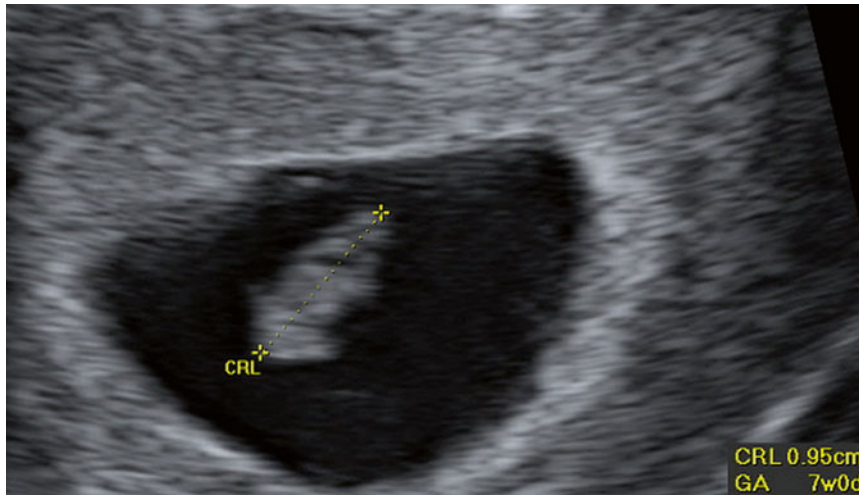

Fig. 6.3 Measurement of the crown-rump length at 7 weeks of gestation

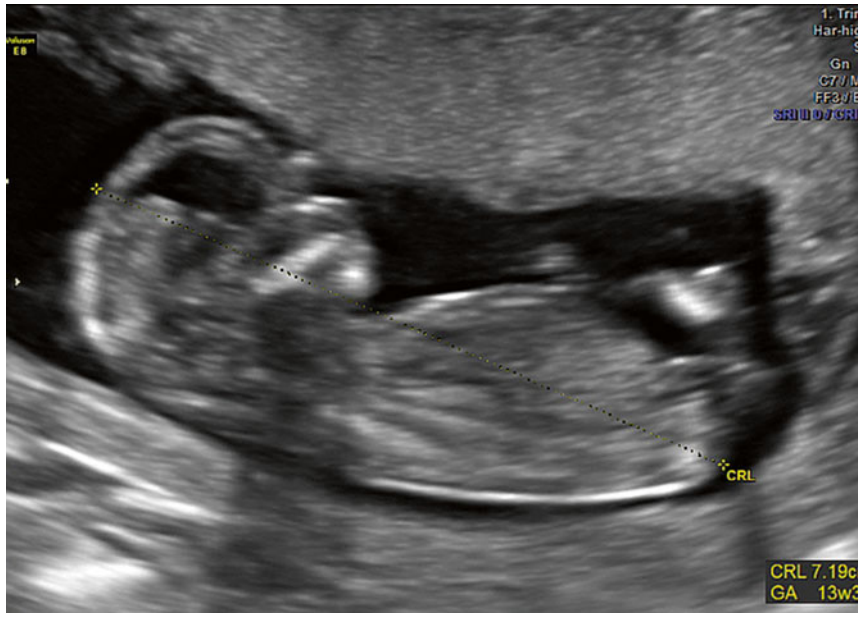

Fig. 6.4 Measurement of the crown-rump length at 13 weeks of gestation. Note the fluid between the fetal chin and chest, confirming that the fetus is not flexed

requires several elements to be in place, including suitable equipment, counseling and management, as well as operators with specialized training and continuing certification [5]. First-trimester evaluation of the fetal nasal bone, screening for tricuspid regurgitation, and Doppler evaluation of the ductus venosus can also be used to screen for aneuploidy.

Other Intrauterine and Extrauterine Structures

There is a general consensus that the uterus, cervix, adnexa, and cul-de-sac region should be examined, and pathologic findings such as abnormalities of uterine shape, fibroids, and adnexal masses should be imaged and documented. The ISUOG guidelines further recommend that the area between the bladder and the uterine isthmus be scrutinized in women with a prior cesarean section. They also recommend that the echo-structure of the placenta should be evaluated, and that placenta previa should not be reported at this stage [5].

Documentation

The AIUM offers specific guidelines regarding documentation of ultrasound examinations [14]. There should be a permanent record of the ultrasound examination and its interpretation. Appropriately labeled relevant images should be recorded in a retrievable format. A signed final report of the ultrasound findings is included in the patient's medical record and is the definitive documentation of the study. Final reports should be available within 24 h of completion of the examination or, for non-emergency cases, by the next business day. Specific documentation requirements will vary depending on the type of exam, indication, findings, and whether or not any associated procedures were performed. If the results of the examination are important and

Table 6.3 ISUOG suggested anatomical assessment at time of 11–13 + 6-week scan[a]

Organ/ anatomical area	Present and/or normal
Head	Present Cranial bones Midline falx Choroid-plexus-filled ventricles
Neck	Normal appearance Nuchal translucency thickness (if accepted after informed consent and trained/ certified operator available)[b]
Face	Eyes with lens[b] Nasal bone[b] Normal profile/mandible[b] Intact lips[b]
Spine	Vertebrae (longitudinal and axial)[b] Intact overlying skin[b]
Chest	Symmetrical lung fields No effusions or masses
Heart	Cardiac regular activity Four symmetrical chambers[b]
Abdomen	Stomach present in left upper quadrant Bladder[b] Kidneys[b]
Abdominal wall	Normal cord insertion No umbilical defects
Extremities	Four limbs each with three segments Hands and feet with normal orientation[b]
Placenta	Size and texture
Cord	Three-vessel cord[b]

[a]Reprinted from ISUOG Practice Guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2013;41(1):102–113, with permission from John Wiley & Sons
[b]Optional structures

unexpected, or require urgent intervention, communication should occur directly between the interpreting physician and the patient's health care provider.

Training Guidelines

The ISUOG has published recommendations for basic training in obstetric and gynecologic ultrasound [15]. It states that formal basic teaching should include three steps: theoretical training, practical training, and examination. Theoretical training is primarily didactic and should cover physics, basics of diagnostic ultrasound, and pertinent clinical concepts. This is followed by practical training with formal supervision, which should include a method of confirming that ultrasounds were performed and documented in a standardized way. The examination should assess theoretical knowledge and may be complemented by a practical examination. The AIUM has published training guidelines for physicians who evaluate and interpret diagnostic obstetric ultrasound examinations [16]. A physician should be involved with the performance, evaluation, interpretation, and reporting of a minimum of 300 diagnostic obstetric ultrasound examinations during completion of an approved training program. For physicians who did not receive ultrasound training during residency and/or fellowship, a minimum of 50 AMA PRA Category I Credits dedicated to diagnostic obstetric ultrasound and involvement with at least 300 exams under the supervision of a qualified physician within a 36 month period is recommended.

Cleaning and Preparing Transducers

The AIUM has published guidelines for cleaning and preparing ultrasound transducers between patients, including specific procedures for cleaning and disinfection [17]. External probes that only come into contact with clean, intact skin require cleaning after each use. Internal probes should be covered for each exam. Variable rates of leakage have been reported with both condoms and commercially available covers and therefore high-level disinfection of the probe is required after each use. Interestingly, condoms have lower leakage compared to commercially available probe covers and also have better acceptable quality levels.

Teaching Points

- Guidelines and recommendations for the performance of first-trimester ultrasound have been developed and published by several societies and organizations.
- Components of a standard first-trimester examination are assessment of pregnancy location, fetal number, fetal viability, measurements, determination of gestational age,

and assessment of other intrauterine and extrauterine structures. Assessment of fetal anatomy and fetal aneuploidy assessment may be appropriate for some patients.

- The first trimester is the optimum time to determine chorionicity and amnionicity, which are critical for management of multifetal pregnancies.
- Findings diagnostic of pregnancy failure include a crown-rump length (CRL) of ≥7 mm and no heartbeat, mean sac diameter (MSD) of ≥25 mm and no embryo, absence of an embryo with a heartbeat ≥2 weeks after a scan that showed a gestational sac without a yolk sac, and absence of an embryo with a heartbeat ≥11 days after a scan that showed a gestational sac with a yolk sac.
- Discrepancies between ultrasound dating and LMP dating that support re-dating based on CRL measurement are more than 5 days at ≤8 6/7 weeks, and more than 7 days from 9 0/7 weeks to 13 6/7 weeks.

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Normal First Trimester of Pregnancy

7

Kalesha Hack and Phyllis Glanc

Introduction

The first trimester conventionally refers to the stage of pregnancy occurring prior to 14 weeks gestational age (GA). First-trimester ultrasound may be used to refer to all scans performed prior to the 14-week mark [1] or to scans occurring between confirmation of an intrauterine pregnancy and 13 + 6 weeks gestation [2]. With the advent of highly sensitive home pregnancy tests, more women are presenting for a dating ultrasound before ultrasound is able to show confirmatory evidence of an early intrauterine pregnancy [3]. For this reason, we have chosen to include a discussion of all ultrasounds performed in a woman with a positive β-subunit of human chorionic gonadotropin (β-hCG) pregnancy test prior to 14 weeks in this chapter.

All dates in this chapter are referred to in menstrual age, which, hereafter, is considered synonymous with GA. GA is defined as the conceptual age +2 weeks. Pregnancy dating can also be described based on timing of conception, known as the conceptual age or embryonic age, where day 1 refers to fertilization. This dating method may be used by assisted reproductive technology specialists.

There are several important stages in early pregnancy development that occur before they can be resolved by current commercial ultrasound technology (see also Chap. 4). Fertilization typically takes place around day 14 of the menstrual cycle, when the sperm and mature ovum unite to form a zygote in the outer portion of the fallopian tube. Initially, the zygote undergoes rapid cellular division and migrates towards the uterus. Implantation typically is complete by 10 days post fertilization and, in a normal pregnancy, occurs within the central portion of the uterine cavity. The embryo begins to flatten out and form a bilaminar disc that lies between the amniotic cavity and exocoelomic cavity. The primitive yolk sac develops at 9 days post fertilization; however, it is not visible sonographically.

The primitive yolk sac subsequently breaks off and is extruded, around 4 weeks GA, to form the secondary yolk sac, which can be seen at early ultrasound. Subsequent use of the term yolk sac in this chapter refers to the secondary yolk sac. In the fifth gestational week, gastrulation occurs and results in the formation of the three germ cells layers: ectoderm, mesoderm and endoderm, each giving rise to different organ

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systems. Closure of the neural tube is generally completed by the end of the sixth week. The developing heart begins to form in week 5 of the pregnancy. Development of the internal and external organs occurs during the first 8–10 weeks of pregnancy, known as the *embryonic period* or *organogenesis*. Prior to the end of the tenth week, the developing pregnancy is referred to as an *embryo*. After this time, once the organogenesis phase is completed, the term *fetus* is used.

Gestational Sac

The earliest sonographically visible evidence of an intrauterine pregnancy is the appearance of an intrauterine gestational sac [1, 4, 5]. With modern high-frequency transvaginal transducers, the gestational sac can first be seen as early as 4 weeks 1 day gestation and is typically seen around 4.5–5 weeks at which time it measures 2–3 mm [6–9]. The gestational sac is a round or ovoid fluid-filled structure identified within the central echogenic portion of the uterus, i.e., the decidualized endometrium. On closer inspection, one can identify that the sac is eccentrically located within the decidua, as opposed to in the endometrial cavity itself (Fig. 7.1a–c).

An important distinction in early pregnancy ultrasound is the ability to differentiate a true intrauterine gestational sac, before the yolk sac or embryo is seen, from an intrauterine fluid collection such as a subendometrial cyst, decidual cyst or fluid collection in the setting of an ectopic pregnancy. Careful interrogation will demonstrate that subendometrial cysts are external to the decidualized endometrium (Fig. 7.2). A decidual cyst is also a benign finding but is more challenging to distinguish from an early IUP. The key distinction will depend on the relationship of the early IUP, which should abut the interstitial line of the collapsed endometrial cavity (see Fig. 7.1d), whereas the decidual cyst may not be anatomically related to the collapsed endometrial cavity. In cases where there is doubt, follow-up imaging will demonstrate appropriate growth of the early IUP gestational sac, with development of a yolk sac to confirm an early IUP.

It is equally important to ensure the "cyst" is not actually within the endometrial cavity. In most cases, fluid within the endometrial cavity can be distinguished from fluid outside of the endometrial cavity on the basis of shape, location and contents. Whereas endometrial cavity fluid collections may be angular, complex with internal echogenic debris, or elongated, conforming to the uterine cavity, the early gestational sac will be anechoic and typically rounded or ovoid [10]. In cases where there is uncertainty, the differential diagnosis will include a pregnancy of unknown location or intracavitary fluid collection, accompanying early pregnancy loss.

Recent studies have shown that intrauterine fluid, commonly referred to as a "pseudogestational sac," in the setting of ectopic pregnancy occurs much less frequently than previously thought and may be seen in only around 10 % of ectopic pregnancies [11, 12]. Doubilet et al. reported in an editorial on pregnancy of unknown location that given the relatively low incidence of ectopic pregnancy (approximately 2 %) and low likelihood of intrauterine fluid with an ectopic pregnancy, the probability that any intrauterine fluid collection in a woman with a positive pregnancy test represents a gestational sac is 99.5 % [13]. This has led to a change in thinking with respect to early pregnancy such that, **in the absence of sonographic evidence of ectopic pregnancy, any fluid collection with curved edges in a woman with a positive pregnancy test should be thought of as an early intrauterine gestational sac** [13]. In this setting, follow-up imaging can be obtained, to confirm subsequent appearance of embryonic structures including a yolk sac and an embryo with cardiac activity. The role of follow-up β-hCG serology is this setting is discussed separately.

The **double sac sign (DSS)** and **intradecidual sign (IDS)** have historically been described as useful in differentiating a true IUP from a non-gestational intrauterine fluid collection [14, 15]. The DDS, first described in 1982, refers to the appearance of two echogenic rings around the

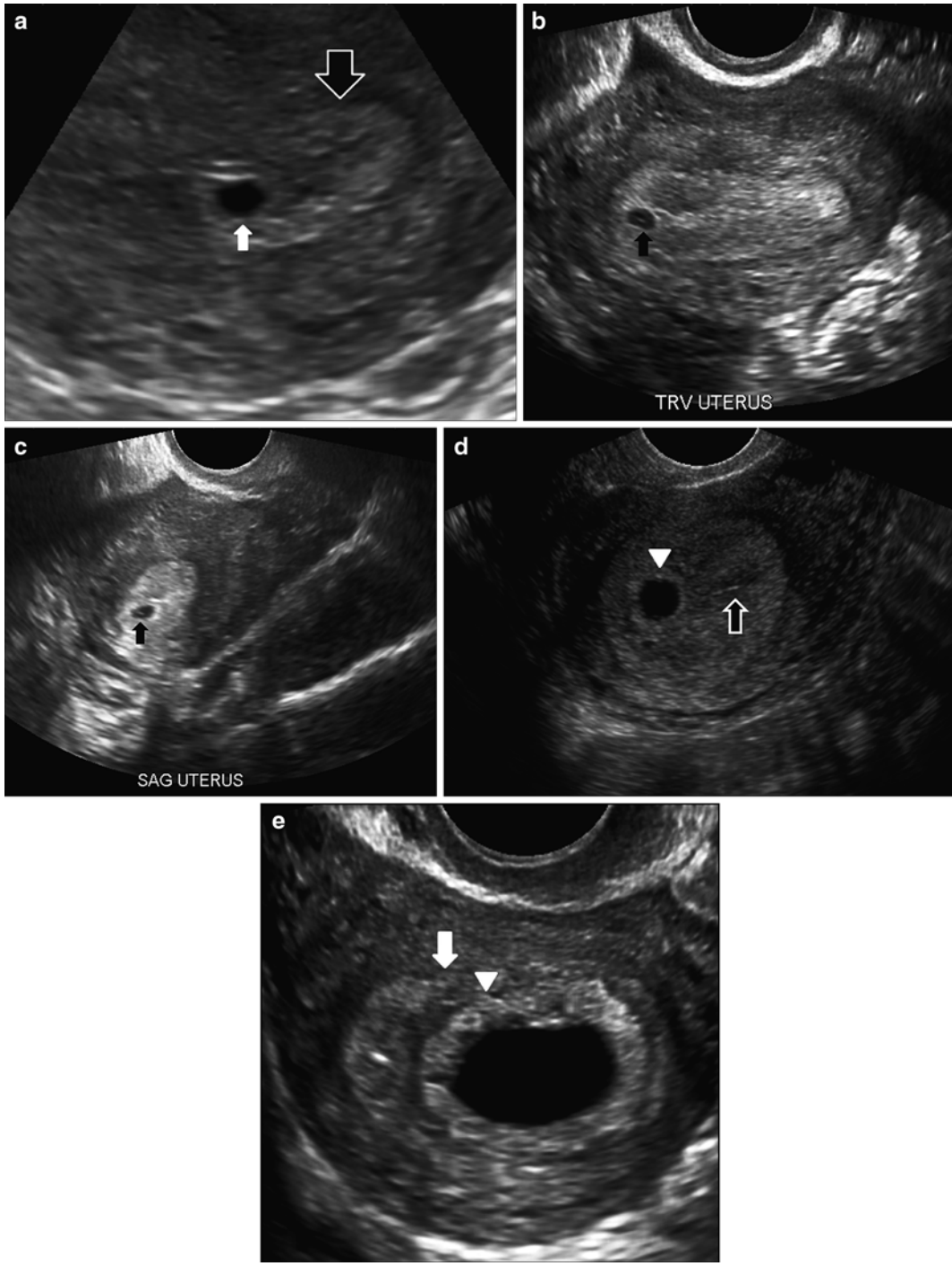

Fig. 7.1 Normal early gestational sac. (**a**) Transabdominal transverse image at 5 weeks, 1 day, showing an apparently empty early gestational sac (*white arrow*) eccentrically located within the decidua (*black arrow*). Transvaginal transverse (**b**) and sagittal (**c**) images at 5 weeks, 1 day can show the yolk sac within the early gestational sac, thus confirming an early IUP. (**d**) Transvaginal transverse image at 5 weeks, 1 day shows an eccentric round fluid collection with an echogenic rim (*white arrowhead*) adjacent to the echogenic line representing the collapsed endometrial cavity (*black arrowhead*) demonstrating the "intradecidual sign." (**e**) Transvaginal transverse image at 6 weeks, 5 days, showing an intrauterine fluid collection surrounded by two concentric echogenic rings forming the so-called "double-sac sign"

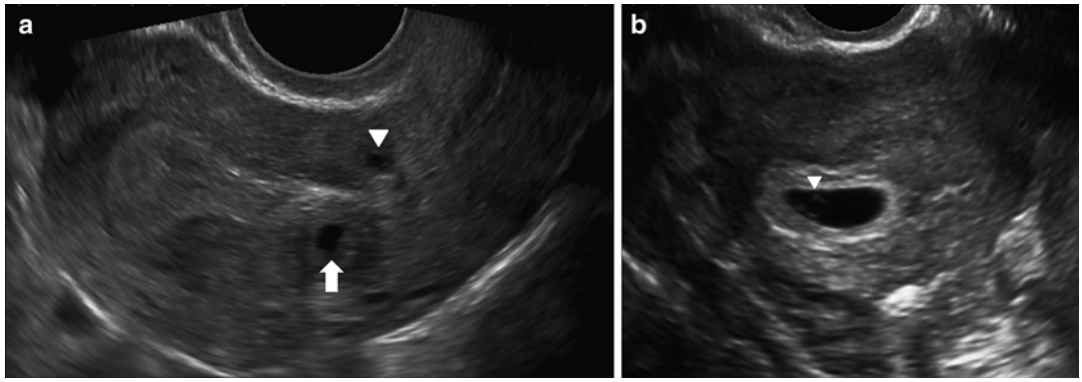

Fig. 7.2 Subendometrial cysts in a patient with a positive pregnancy test and unknown dates, transvaginal images. (**a**) Sagittal image shows a rounded fluid collection posterior to the hyperechoic decidualized endometrium (*arrow*) and a similar cyst anterior to the endometrium in the lower uterine segment (*arrowhead*). These are incidental findings. No gestational sac was seen at this time. (**b**) Follow-up study 9 days later shows intrauterine gestational sac with visible yolk sac (*arrowhead*)

gestational sac felt to represent the inner and outer layers of the decidua, the decidua capsularis and decidua basalis (see Fig. 7.1e) [15]. The IDS, initially described in 1986, refers to a fluid collection with an echogenic rim in an eccentric location on one side of the uterine cavity (see Fig. 7.1d) [14]. Both of these signs were initially described on transabdominal ultrasound and considered to be early reliable signs of an IUP with the DSS seen in 77 % of the initial study population with an IUP and the IDS seen in 92 % [13–15]. Currently, with the advent of high-resolution, high-frequency transvaginal transducers, subsequent studies have shown that in normal IUP the DSS may be absent in 50–60 % and the IDS absent in up to 50 % [13, 16, 17]. With improvements in technology, it is no longer infrequent that the yolk sac is visible prior to DSS and IDS and, consequently, these signs are now felt to be of limited utility. While their presence may be useful in confirming an IUP, the absence of a DSS or IDS should not be used to exclude one [18].

Measurement of the Gestational Sac[1]

Measurements of the gestational sac can be obtained and used to estimate gestational age and predict appearance of normal embryonic structures. The mean sac diameter (MSD) is obtained by averaging the transverse, sagittal and anteroposterior dimensions of the gestational sac and can be correlated with expected GA and with β-hCG levels (Fig. 7.3). There is variability in gestational sac size measurements between different observers. This was highlighted in a recent study of 54 patients by Pexsters et al. [19] which reported the interobserver variability for MSD as being up to ±19 %. Expected rate of growth of the gestational sac has previously been reported as approximately 1 mm per day [7]. However, in a study of 359 women, Abdallah et al. [20] found overlap in MSD growth rate in viable and nonviable early IUP and were unable to define a rate of gestational sac size that can be considered normal in early pregnancy [20]. A small gestational sac with less than 5-mm difference between crown-rump length and gestational sac length has been referred to as first-trimester oligohydramnios and considered to be associated with poor outcome [21]. However, this has only been examined in a small population and as an isolated finding likely warrants follow-up imaging (Fig. 7.4).

Mean Sac Diameter and Viability

Much attention has been given to the maximum size at which an empty gestational sac, i.e., a sac without a visible yolk sac or embryo, can be

[1] See also Chap. 9.

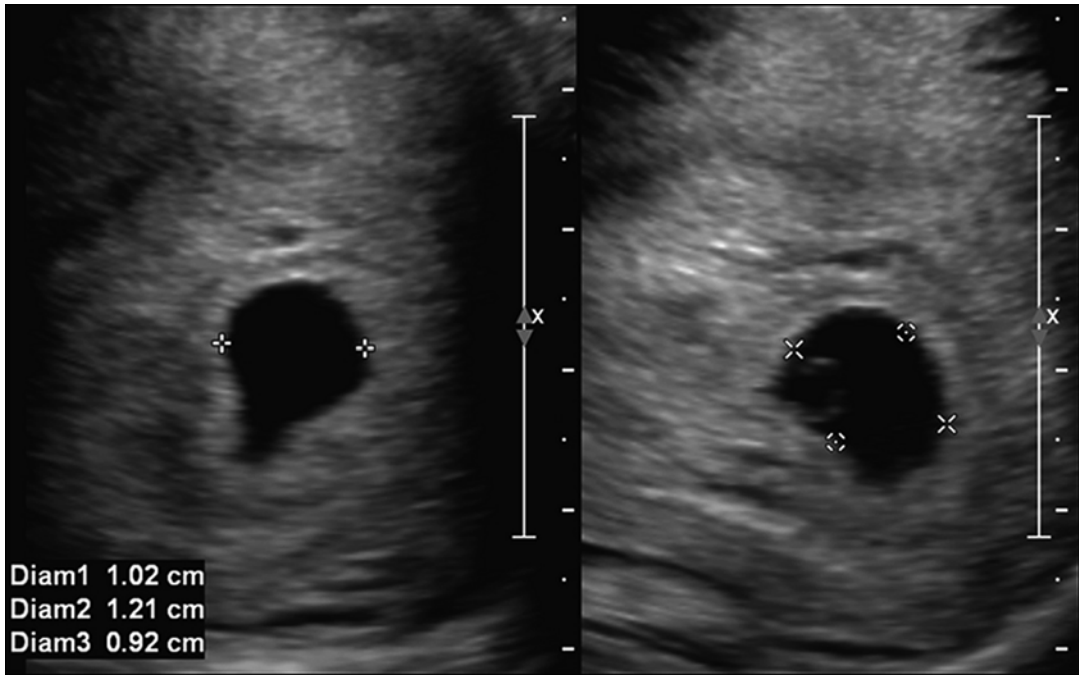

Fig. 7.3 Mean sac diameter. Transabdominal sagittal and transverse images at 5 weeks, 5 days of the uterus, measuring the gestational sac in three orthogonal dimensions, which are averaged to obtain the mean sac diameter. Care should be taken to place calipers directly on the white line around the sac to ensure accurate measurements

considered normal. While a yolk sac is usually seen with an MSD > 8 mm, the MSD at which a yolk sac and embryo can be sonographically detected is variable and caution should be exercised if using MSD to determine viability [22]. Historically, the upper limit at which an empty gestational sac was considered a normal early pregnancy finding was a transvaginally measured MSD between 16 and 20 mm [23, 24]. However, several recent studies have shown that a small percentage of viable pregnancies may exist with empty sac size up to 18–19 mm [25, 26] and given interobserver variability in sac size measurement, **an empty gestational sac should be considered a potentially normal early pregnancy finding up to an MSD of 25 mm on transvaginal ultrasound** [20, 23, 24, 26, 27]. This is discussed further in Chap. 10 which refers to new discriminatory criteria for defining early viability. Detection of peritrophoblastic flow demonstrating high velocity and low impedance around the gestational sac is a normal finding that has been described as an aid in confirming a very early intrauterine pregnancy [28]. However, caution is recommended in the use of color and, particularly, spectral Doppler imaging in early pregnancy, due to increased power output and potential risk to developing pregnancy [8, 29].

Gestational Sac Appearance and β-hCG in Early Pregnancy

A gestational sac is usually visible in an intrauterine pregnancy when the β-hCG level is between 1000 and 2000 mIU/ml [4]. Historically, much attention has been paid to the concept of a discriminatory β-hCG level above which an intrauterine gestational sac should always be seen in a normal IUP. This number was initially around 2000 mIU/ml, however, it is now recognized that there is considerable overlap of β-hCG levels in viable IUP, nonviable IUP and ectopic pregnancy [30, 31]. Doubilet et al. have reported that, in rare instances, even with an absent gestational sac on transvaginal ultrasound and β-hCG

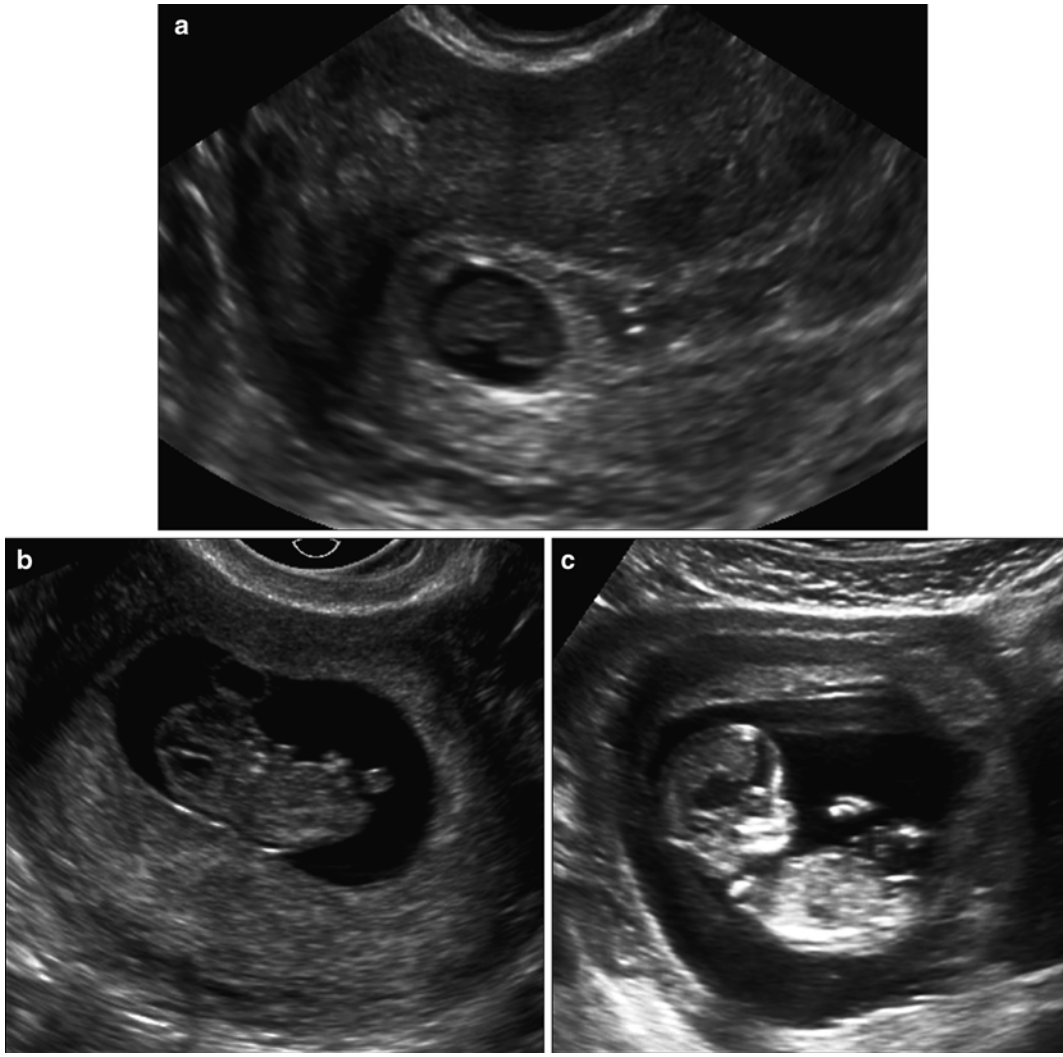

Fig. 7.4 First-trimester oligohydramnios. (**a**) Transvaginal image at 7 weeks, 4 days, showing small sac size (MSD 12.4 mm) for CRL (8.1 mm) in keeping with "first-trimester oligohydramnios." (**b**) Transvaginal follow-up scan at 8 weeks, 1 day shows live embryo with persistent discordant GS size. (**c**) Transabdominal image at 12 weeks, 0 days shows live fetus with interval growth of both sac and fetus; however, sac continues to be small. A follow-up study at 16 weeks demonstrated normal fetal growth and fluid

level >4000 mIU/ml, follow-up ultrasound can show a normal pregnancy [30]. Practically speaking, it is unlikely to have a normal IUP development when no gestational sac is seen with a β-hCG level >3000 mIU/ml. This cannot, however, be considered diagnostic criteria for early pregnancy loss with 100 % specificity. Consequently, the use of a single discriminatory β-hCG level to guide management in the setting of pregnancy of unknown location (PUL) is not recommended [30, 32]. There is emerging evidence that the incremental increase in serum β-hCG over 48 h, expressed as a ratio, may be a useful predictor of IUP when ultrasound findings are inconclusive [33–35]. Recently, Bignardi et al. [33] have reported that a β-hCG ratio >2.0 is suggestive of a viable IUP with sensitivity of 77 %, specificity of 96 % and a positive predictive value of 87 %.

However, the use of β-hCG ratio as a predictor of viability in the setting of early pregnancy is not yet routine practice in all centers.

Yolk Sac

The appearance of the yolk sac provides the first *definitive* confirmation of an intrauterine pregnancy. **Although visualization of the gestational sac, the double decidual sac sign, or the intradecidual sign may increase the likelihood of an IUP, they are not as accurate at confirming an IUP as detection of the yolk sac**.

The yolk sac can first be visualized within the gestational sac at approximately 5.5 weeks gestation [1, 5, 8, 36] as a thin echogenic circular ring within the gestational sac. It is usually visible by the time the MSD reaches 8 mm. If the yolk sac is not identified by this stage, a careful interrogation of the gestational sac with image optimization may assist in the ability to detect it. These may include narrowing the sector width, image zoom, appropriate placement of the focal zone, choice of a higher frequency, or other vendor specific post-processing settings (Fig. 7.5).

Normal yolk sac measurement between 5 and 10 weeks GA is around 5 mm [8]. An enlarged yolk sac greater than 5 mm may be associated with poor pregnancy outcome. As an isolated finding, however, it cannot be considered definitely abnormal (Fig. 7.6) [37].

Embryo

The embryo is first visualized alongside the yolk sac at approximately 6 weeks gestation. Initially, it appears as a featureless linear echogenic structure without discernible limb buds and with no distinct cranial or caudal end (Fig. 7.7a). At this stage a quantitative assessment of the embryo is achieved by obtaining the longest length measurement. Once the crown and rump are distinguishable, it is ideal to acquire the crown-rump length (CRL), which is defined as the longest length excluding the limbs and yolk sac (Fig. 7.7b). The CRL can be measured transabdominal or transvaginal. The ideal plane of measurement is midsagittal, with the embryo or fetus in a neutral position. Presence of fluid between the fetal chin and chest can be used as a sign to ensure that the fetus is not hyperflexed [2]. In practical terms, prior to 7 weeks gestation, measurement is actually of the longest length of the embryo that can be seen, but, after 7 weeks, a concerted effort should be made to measure the embryo in the midsagittal plane, excluding the

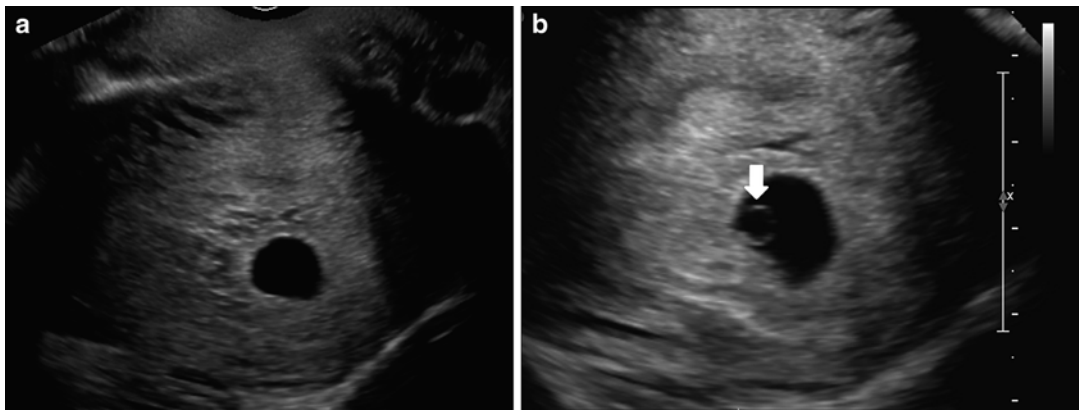

Fig. 7.5 Normal yolk sac at 6 weeks, 1 day. (**a**) Transvaginal transverse image shows an apparently empty gestational sac. (**b**) Transvaginal transverse zoomed image with narrowed sector width is able to detect a circular echogenic ring, which represents the yolk sac (*white arrow*) and thus confirms an early IUP

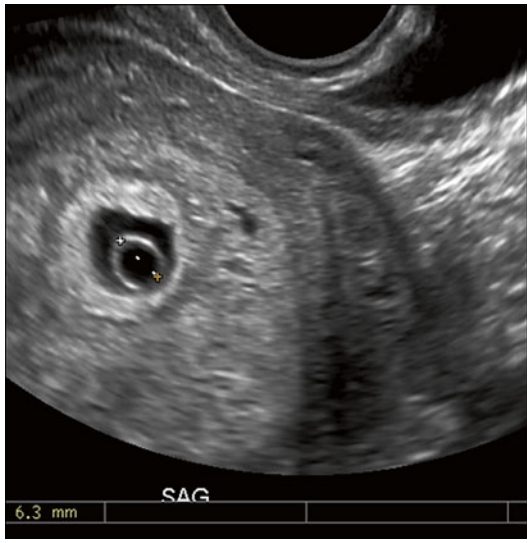

Fig. 7.6 Transvaginal sagittal image of large yolk sac at 5 weeks, 6 days shows enlarged yolk sac measuring 6 mm

yolk sac [38] (Fig. 7.7c). The smallest detectable embryo transvaginally has a CRL of 1–2 mm. Normograms are available to correlate CRL with gestational age [39–42]. A recent 2014 publication by Papageorghiou et al. provides a CRL chart for pregnancy dating, based on a multicenter international trial, thus providing a first international standard for evaluating CRL linear growth in first trimester [43].

Embryonic and Fetal Cardiac Activity

Embryonic cardiac activity (ECA) is usually visible as soon as the embryo is detectable and can be seen with a CRL as small as 1 mm [4]. **Although, ECA is virtually universally identified by CRL**

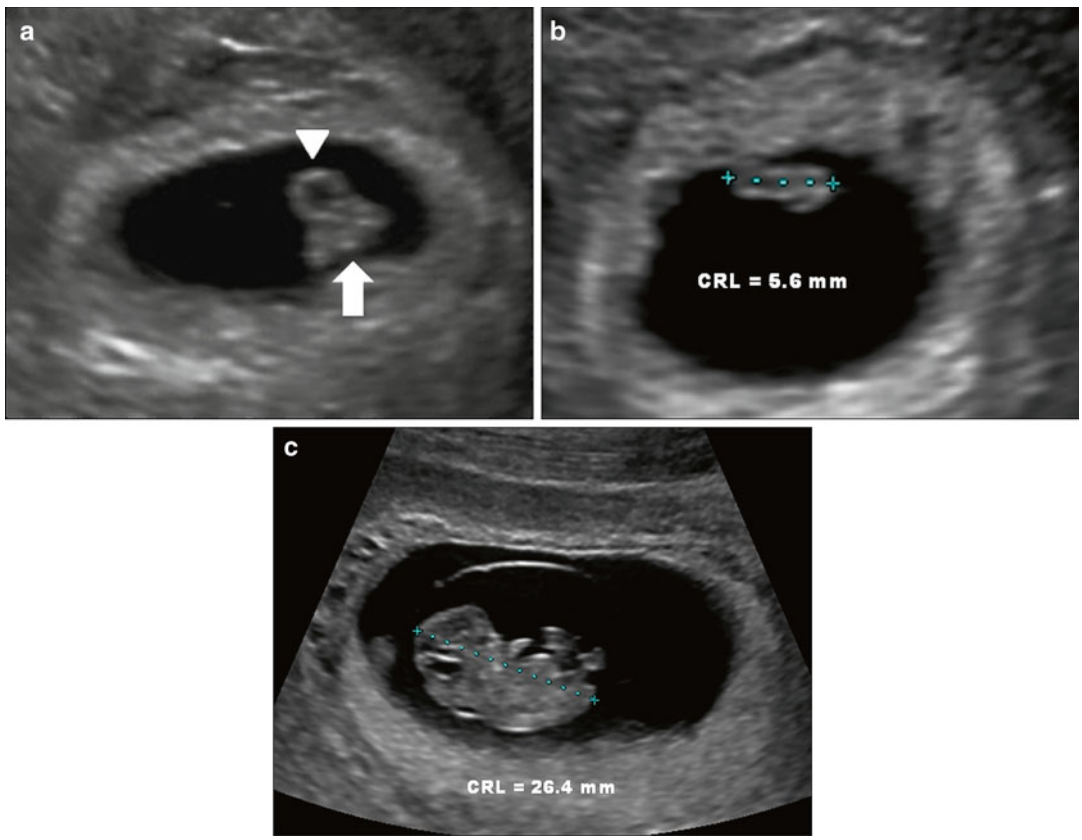

Fig. 7.7 Early embryo and crown-rump length. (**a**) Transvaginal image at 6 weeks, 6 days, showing yolk sac (*arrowhead*) and embryo (*arrow*). (**b**) Embryo at 6 weeks, 2 days with CRL of 5.6 mm. The maximum linear length is measured. (**c**) Embryo at 9 weeks, 2 days with CRL of 26.4 mm. Note that distinct cranial and caudal ends are now visible. Calipers must be carefully placed to exclude yolk sac and flexed limbs

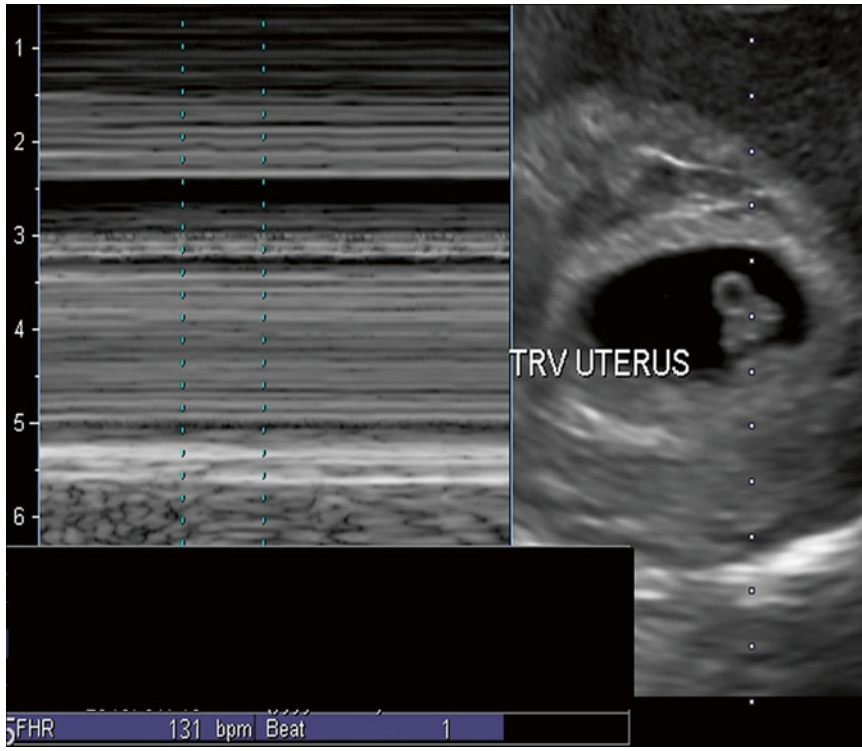

Fig. 7.8 M mode of embryonic cardiac activity at 6 weeks, 6 days. Transvaginal image showing embryonic cardiac activity detected with M mode

of 4–5 mm, the absence of ECA cannot be considered abnormal until the embryo reaches 7 mm [23, 24]. This number is chosen to achieve as close to 100 % specificity as possible for diagnosing early pregnancy loss based on absence of embryonic cardiac activity while taking into account the potential ±15 % interobserver variability in CRL measurement [44].

Embryonic cardiac activity is documented using motion mode (M mode) to determine a heart rate (Fig. 7.8). ECA is considered normal if greater than 100 beats per minute (bpm). Doubilet et al. [45] suggested a lower limit of normal embryonic heart rate of 100 bpm up to 6.2 weeks gestation and 120 bpm between 6.3 and 7 weeks. Embryonic heart rates <100 bpm were thought to be associated with an increased risk of demise. However, a recent review of early first-trimester pregnancies with slow embryonic heart rate reveals that this may not necessarily be a poor prognostic factor [45–47]. High embryonic heart rate in early pregnancy has been defined by Benson et al. [48] as >135 bpm before 6.3 weeks and >155 bpm between 6.3 and 7 weeks. This generally has a good prognosis with high likelihood of normal outcome.

Multiple Gestations and Chorionicity[2]

Globally twins are approximately 1–3 % of all pregnancies [49]. Twin rates have doubled between 1980 and 2009 from 18.9 to 33.2 per 1000 births [50]. In some areas of the USA the prevalence of multiple gestations is as high as 1 in 30 pregnancies. This is thought to be related to a combination of assisted reproductive technologies and increasing maternal age. Two-thirds of twin pregnancies are dizygotic and one-third is monozygotic. The rate of intrapartum complications including pregnancy loss due to twin-twin

[2] See also Chap. 14.

transfusion syndrome or selective fetal growth restriction is far greater in monochorionic twins [51]. For optimal care, monochorionic pregnancies should be identified as early as possible to allow for closer surveillance and early detection of these conditions. **Assignment of chorionicity is therefore a mandatory and vital component of first-trimester ultrasound with multiple gestations**. However, surprisingly in a review by Wan et al., only 44 % of pregnancies referred to a tertiary care center had accurate diagnosis of amnionicity and chorionicity [52]. It is therefore important that practitioners be familiar with signs used to assess amnionicity and chorionicity in the first trimester.

The best time to determine chorionicity is prior to 14 weeks gestational age [51]. The classic features to determine a dichorionic gestation include two separate gestational sacs or placental masses, a thick inter-twin membrane in association with the lambda (λ) sign and different fetal genders. The λ sign refers to a triangular shaped projection of tissue which extends into the inter-twin membrane and is synonymous with the "twin-peak" sign (Fig. 7.9).

Prior to 10 weeks the presence of two distinct, separated gestational sacs will confirm a dichorionic–diamniotic (DCDA) pregnancy. After 10 weeks, the most reliable signs for assessing chorionicity are a combination of placental number and the λ sign [51] given that gender cannot be reliably be determined prior to 12 weeks. In a study of 648 twin pregnancies, the number of placental masses and the presence of either the T or λ sign is virtually 100 % accurate for determining chorionicity between 11 and 14 weeks [51].

With respect to differentiating monoamniotic from diamniotic pregnancies, it is important to recognize that the temporal development of the yolk sac and the amnion is variable [53]. The appearance of the amniotic sac can be as late as 8–10 weeks with the thin membranes making it challenging to identify, even with the higher resolution of transvaginal ultrasound (Fig. 7.10). In the setting of multifetal pregnancies, the number of yolk sacs was previously thought to be a reliable way to assign amnionicity; however, it is less reliable than once presumed [53, 54]. While the presence of two yolk sacs is highly predictive of a diamniotic pregnancy and is seen in approximately 85 % of monochorionic–diamniotic (MCDA) twins, the presence of only one yolk sac can be seen with both monoamniotic and diamniotic twin pregnancies [53]. On rare occasion a monochorionic–monoamniotic (MCMA) twin pregnancy may present with two yolk sacs. If it is uncertain that a membrane is present separating the fetuses, it is prudent to repeat the test 1–2

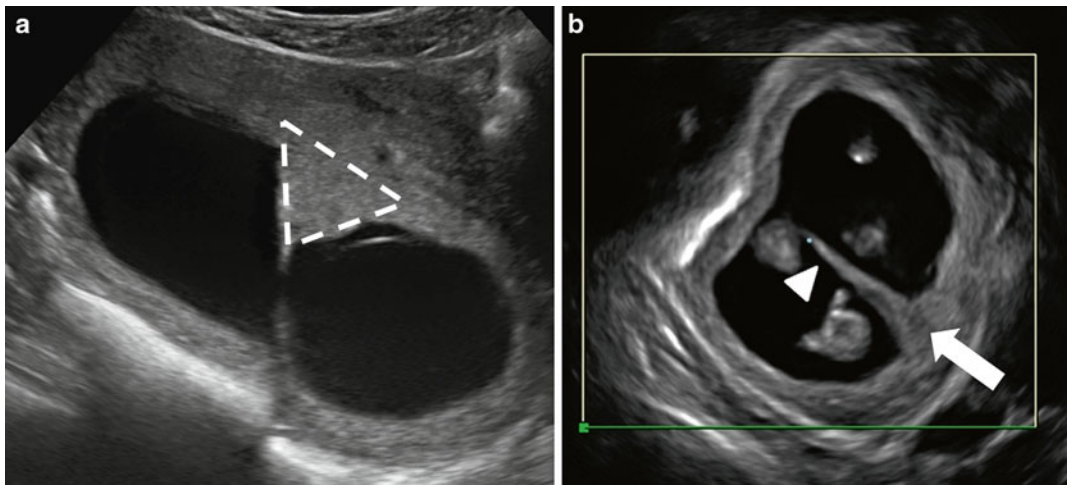

Fig. 7.9 Lambda sign in 11 weeks, 3 days dichorionic twin gestation. (**a**) Transabdominal image showing *triangular shaped* tissue projecting into inter-twin membrane (*white outline*) representing the lambda sign. (**b**) 3D representation showing lambda sign (*arrow*) and thick inter-twin membrane (*arrowhead*)

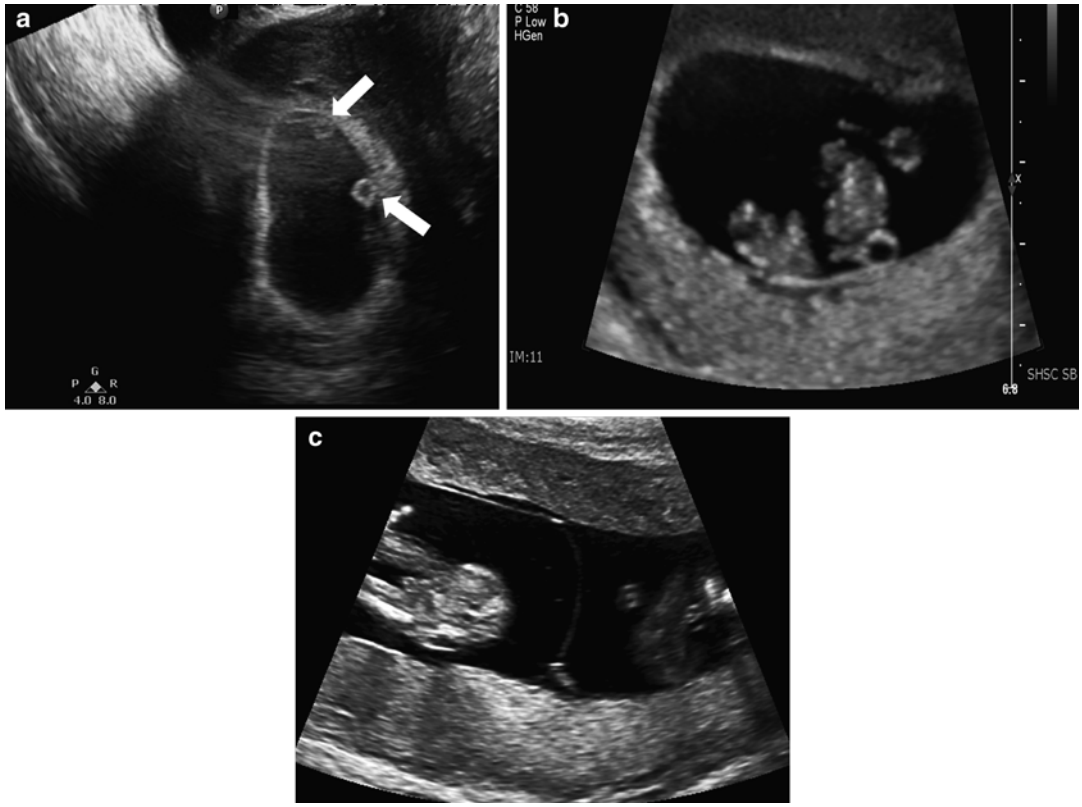

Fig. 7.10 Early MCDA twin pregnancy. (**a**) Transvaginal transverse image at 7 weeks, 0 days shows two yolk sacs (*arrows*) in keeping with twin gestation. No dividing membrane is seen; however, amnionicity cannot be definitely assigned at this early stage. (**b**) Follow-up study at 8 weeks showing two yolk sacs and two embryos. A dividing membrane is not yet identified. (**c**) Thirteen-week follow-up shows thin dividing inter-twin membrane confirming MCDA pregnancy

weeks later. Alternatively, direct visualization of umbilical cord entanglement may provide early confirmation of the monoamniotic status of a twin gestation.

Heterotopic Pregnancy

Prior to the more widespread use of assisted reproductive techniques (ART), the presence of an intrauterine gestational sac with a yolk sac was felt to virtually exclude the diagnosis of ectopic pregnancy. Nonetheless, heterotopic pregnancy can occur where an ectopic pregnancy coincides with an otherwise normal IUP. The estimated incidence of this occurrence is between 1 in 8000 and 1 in 30,000 (Fig. 7.11) [55]. The incidence may be higher in gestations after assisted fertility [56] and has been estimated as high as 1 in 100 in this population [40]. Thus, in patients who have undergone ART, despite the presence of an IUP, a thorough interrogation of the adnexae is recommended, to rule out a heterotopic pregnancy.

Early Pregnancy Dating

One of the indications of first-trimester ultrasound is to confirm dating of pregnancy. Accurate pregnancy dating is critical to prenatal management for a variety of reasons including: to prevent preterm induction of supposed postdates pregnancies, to determine viability in the setting

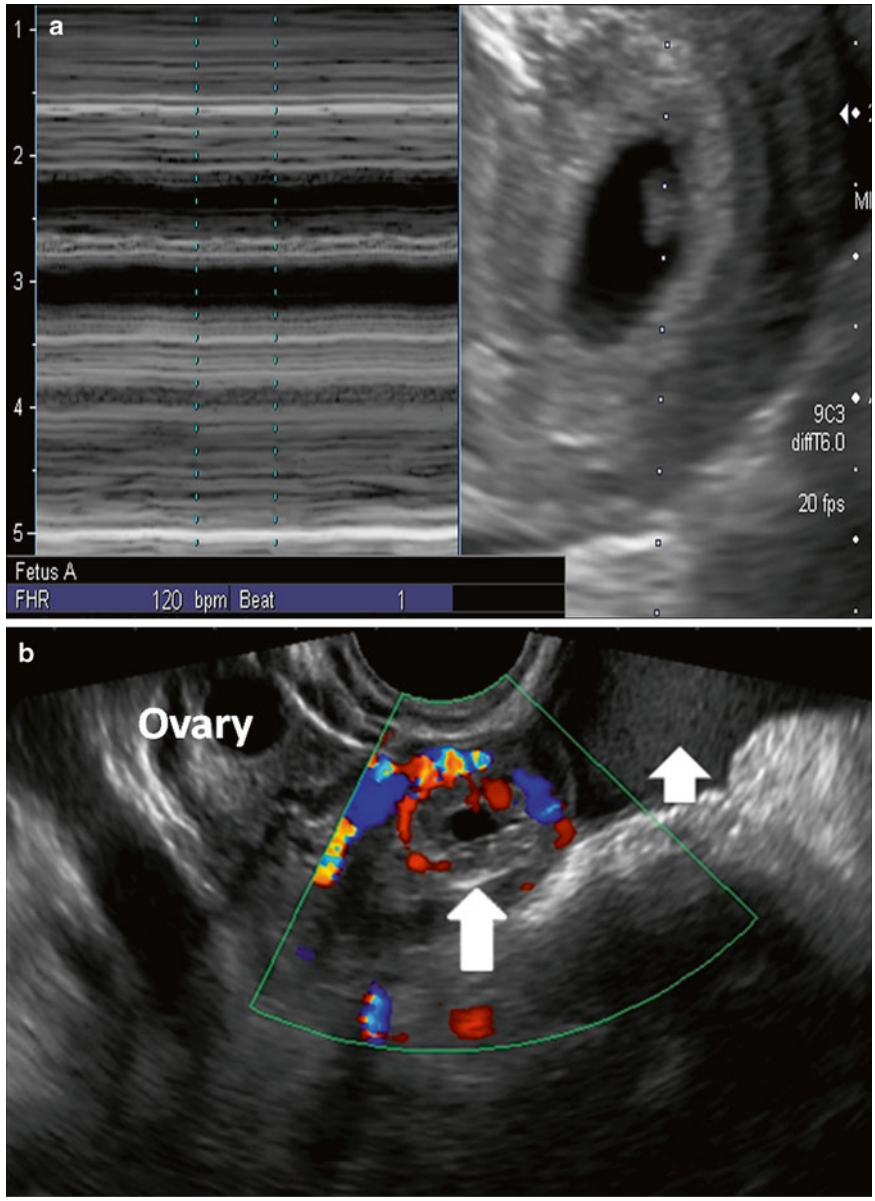

Fig. 7.11 Heterotopic pregnancy. (**a**) Transvaginal image at 6 weeks, 5 days showing live intrauterine pregnancy. (**b**) Transvaginal sagittal image of the right adnexa shows a hypoechoic mass (*long arrow*) surrounded by a vascular echogenic ring, i.e., "ring of fire," separate from the normal ovary with follicles visible at superior margin image. Complex free fluid in keeping with hemorrhagic fluid (*short arrow*) is noted

of premature delivery, to interpret growth patterns, to optimize prenatal screening for aneuploidy and to appropriately time diagnostic interventions such as chorionic villus sampling and amniocentesis [57, 58]. Evidence has shown early ultrasound dating of pregnancy to be more accurate at predicting the expected due date than menstrual history [2, 59, 60]. Pregnancy dating is most accurate in the first trimester and can be determined using MSD, CRL, or fetal biometry. MSD can be used for dating when the embryo is not seen but shows greater variability in predicting

GA compared to CRL [61] and should not be used when an embryo is visible. **The most accurate estimation of gestational age is achieved in the first-trimester by using the CRL somewhere between 8 weeks and 13+6 weeks** [2, 42, 58, 62]. At earlier gestations, the relatively small size of the embryo may lead to more significant measurement error. The reported accuracy of the CRL measurement for dating is within 3–8 days [7], with the most accurate results reported when CRL measures [63] between 7 and 60 mm [41, 42, 62]. CRL continues to be the most reliable predictor of gestational age until 12–14 weeks, when CRL and biometry begin to achieve similar accuracy [64–67]. Based on current recommendations by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), CRL is recommended for dating until the embryo measures 84 mm. Beyond 84 mm, the use of head circumference has been shown to be slightly more accurate than BPD [2]. Given the increased accuracy of ultrasound for pregnancy dating and the clinical importance of accurate dating, it has been suggested that a first-trimester dating ultrasound be performed in all pregnancies [63, 68–71]. Dating of the pregnancy may be performed concurrently with the 11- to 14-week nuchal translucency scan.

Thresholds for Assessing Viability

Recently, new diagnostic criteria have been published with respect to assessing early viability which will be discussed further in Chap. 10. These values have been chosen to include almost all normal pregnancies in an effort to "do no harm" and prevent the small risk of erroneously reporting early pregnancy loss in the setting of a viable pregnancy.

The criteria, which are based on transvaginal ultrasound assessment, have increased the thresholds at which nonvisualization of ECA and embryonic structures may be considered normal and are summarized as follows:

- Absence of cardiac activity in an embryo < 7 mm *may be normal*.
- Absence of an embryo with an MSD < 25 mm *may be normal*.

Follow-up in 1 week's time is recommended in the above two scenarios.

Nuchal Translucency Evaluation[3]

Assessment of nuchal translucency is routinely offered in many countries, including the USA, as a component of prenatal screening and when combined with maternal age and maternal serum biochemistry (β-hCG and pregnancy associated plasma protein-A [PAPP-A]) can be an effective method of screening for chromosomal abnormalities [72]. Nuchal translucency (NT) refers to the sonolucent area posterior to the fetal neck. For the purpose of prenatal screening, the NT should be assessed between 11 and 13+6 weeks gestational age, when the embryo measures between 45 and 84 mm by transabdominal ultrasound technique. The NT should be seen transabdominally in about 80 % of cases [72]. Transvaginal assessment of the NT can be attempted if visualization is inadequate by transabdominal approach, however, it is more challenging due to limited ability to maneuver the probe to obtain a true midline sagittal image. If the NT is not adequately seen transabdominally, our routine is to either bring the patient back later the same day or on a subsequent day, rather than perform a transvaginal study. However, many centers will prefer to proceed to a transvaginal examination immediately following an unsuccessful transabdominal NT evaluation.

Criteria for NT Measurement

Accurate measurement of nuchal translucency is required to optimize results of screening tests. Both the American Institute of Ultrasound in Medicine (AIUM) and ISUOG have published guidelines outlining proper technique for NT

[3] See also Chaps. 8 and 9.

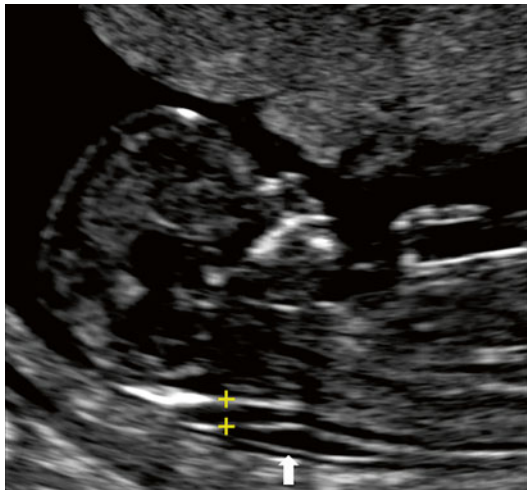

Fig. 7.12 Nuchal translucency at 12 weeks, 0 days. Transabdominal sagittal midline image showing normal nuchal translucency (between calipers). The thin echogenic line of the amnion (*white arrow*) can be seen as separate from the NT

measurement [2, 5]. The NT should be evaluated in the midsagittal plane of the face, defined by visualization of the echogenic tip of the nose and rectangular shape of the palate [2]. The fetus should be in a neutral position, neither hyperflexed nor extended. The image should be magnified, such that the fetal head and upper thorax fill the screen. Margins of the NT edges must be clear enough for proper placement of calipers which should be placed directly on the edges of the NT. Equipment used should allow for precise measurement up to 0.1 mm. The amnion should be seen as a separate echogenic line from the NT (Fig. 7.12). The NT should be measured at the widest space and, if multiple measurements meeting the criteria are obtained, the largest measurement should be used for risk assessment. It is important that individuals who perform a NT evaluation have undergone training and are associated with an appropriate quality assurance program.

Significance of Elevated NT Measurement

Normal nuchal translucency is defined as a measurement less than 3 mm, if the 95th percentile is used or 3.5 mm, if the 99th percentile is chosen [72].

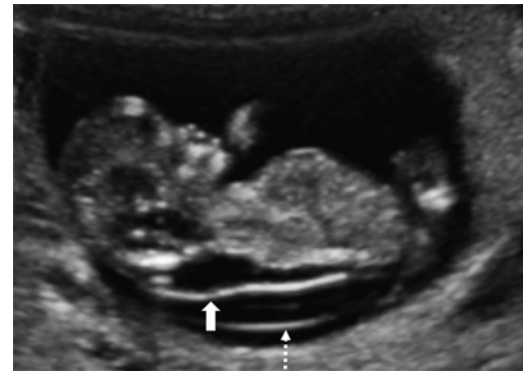

Fig. 7.13 Elevated nuchal translucency in euploid fetus: fetus at 11 weeks, 1 day with abnormal elevated NT measuring 3.9 mm (*arrow*). Note amnion is visualized separate and distinct from amnion (*dashed arrow*). Subsequent cell-free DNA, chorionic villus sampling, early anatomy including echocardiography were normal. The pregnancy continued with normal outcome

Nuchal translucency increases with increasing gestational age and higher measurements are associated with greater risk of abnormality [73]. When combined with maternal age and serology (including PAPP-A and maternal serum β-hCG), NT thickness successfully identified 89 % of fetuses with trisomy 21, with a false-positive rate of 5 % [72]. Elevated nuchal translucency can also be associated with other chromosomal abnormalities, including trisomy 13, 18 and Turner's syndrome [72]. Even in normal karyotype fetuses, an elevated NT confers a greater risk of fetal structural anomalies, most commonly congenital heart anomalies [74]. The prevalence of congenital heart disease with an NT > 95th percentile is 1/48 and is 1/19 with NT >99th percentile [74]. A meta-analysis of 2271 singleton euploid fetuses, with NT > 3 mm at 10–14 weeks, reported structural anomalies in 10.6 % and genetic syndromes and single-gene disorders in 15 % [75]. The prevalence of abnormal outcome was shown to increase with increasing NT measurements.

It is important to note, however, when counselling patients, that not all elevated NT pregnancies are necessarily associated with congenital or structural anomalies (Fig. 7.13). In one report, 90 % of pregnancies with NT measurement below 4.5 mm and normal karyotype resulted in healthy live births [72]. Normal outcome was

seen in 80 % of pregnancies with NT between 4.5 and 6.4 mm and 45 % of pregnancies with NT greater than 6.5 mm [76]. In the previously described meta-analysis evaluating outcome of elevated NT above 3 mm, chromosomally normal fetuses had a 68 % overall chance of normal outcome. Long-term neurodevelopmental outcomes have also been evaluated in children who had an increased fetal NT and normal karyotype. In a systematic review of 17 studies and 2458 patients, there was no significant difference in the rate of neurodevelopmental delay in this group, when compared to the general population., Nonetheless, further large-scale prospective studies are needed to predict neurodevelopmental outcome in this population with greater certainty [77].

Recommendations in the setting of increased NT include detailed early anatomic assessment to look for structural anomalies, fetal echocardiography, and discussion regarding cell-free DNA analysis and/or invasive diagnostic testing such as chorionic villus sampling and amniocentesis.

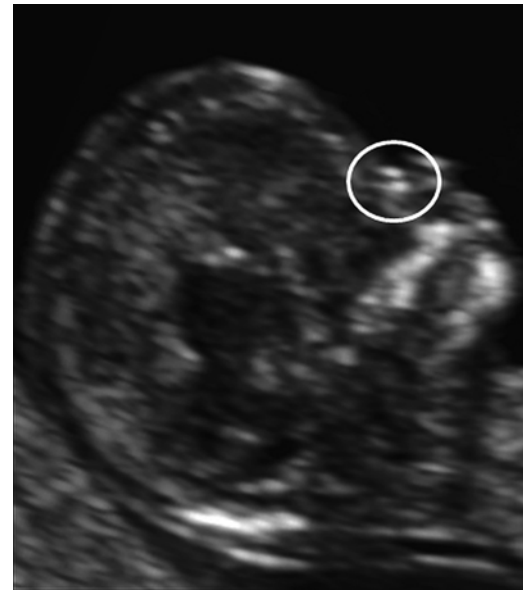

Fig. 7.14 Nasal bone at 12 weeks, 5 days. Transabdominal sagittal midline image shows the nasal bone as an echogenic line posterior to the skin line resulting in two parallel echogenic lines referred to as the "equal sign" (*circle*)

Assessment of the Nasal Bone During the NT Evaluation

Evaluation for presence or absence of the nasal bone can be performed at the time of NT scan [72, 78, 79]. Nasal bone ossification first becomes apparent at a crown rump length of approximately 42 mm [79] or 11 weeks gestation and nasal bone length progressively increases with gestation. Assessment for presence of the nasal bone is performed in the midsagittal plane and, as for NT measurement, requires strict adherence to proper technique and operator experience to be reliable. The nasal bone appears as an echogenic line parallel to and thicker than the echogenic skin line overlying the nasal bridge. It is best seen when the footplate of the transducer is parallel to the long axis of the nasal bone. The two parallel lines of the nasal bone and skin line comprise the "equal sign" (Fig. 7.14). The nasal bone is considered absent if the deeper line is not present. Nasal bone assessment appears to be more difficult than NT assessment. Nevertheless, there are reports that, with adequate training and experience, assessment for presence or absence of nasal bone can be performed with success in up to 99 % of fetuses [80].

Significance of Absent Nasal Bone

As mentioned, an absent nasal bone is seen more frequently in trisomy 21 as compared to the general population. In a study of over 21,000 fetuses between 11 and 14 weeks, absence of the nasal bone was noted in 62 % of fetuses with trisomy 21 as compared to 0.6 % of unaffected fetuses [80]. Absence of nasal bone has been shown to be an independent finding with respect to serum β-hCG and PAPP-A and can, therefore, be added to routine combined prenatal screening for trisomy 21 [79]. When combined with routine NT screening and serum β-hCG and PAPP-A, addition of nasal bone presence may decrease the false positive rate for trisomy 21 from 5 to 2.5 % [79]. Absence of the nasal bone has also been reported in approximately 55 % of fetuses with trisomy 18, 35 % of trisomy 13, and 10 % of Turner's syndrome [81].

However, it is important to be aware that an absent or hypoplastic nasal bone does not necessarily imply pathology and can be a normal variant. The prevalence of absent nasal bone decreases with gestational age and absence of the nasal bone prior to a crown rump length of 42 mm should not be considered abnormal. If there is question of nasal bone absence between 11 and 12 weeks, a repeat scan can be obtained to ensure that lack of visualization represents true absence, as opposed to late ossification. Additionally, there is ethnic variation in presence and size of the nasal bone and an absent nasal bone may be more prevalent in certain ethnic groups, particularly African and Asian populations. A prospective study of nearly 4000 fetuses reported prevalence of absent nasal bone to be 5.8 % in patients of African origin, 3.4 % in patients of Asian origin, and 2.6 % in patients of Caucasian origin [82].

In some instances, the nasal bone may be present but seen to be shortened or hypoplastic. Nasal bone length has not been shown to be a useful first-trimester measurement for screening of trisomy 21 [79].

Screening for Neural Tube Defects at the Time of the NT Evaluation

Neural tube defect with open spina bifida is a relatively uncommon condition affecting approximately 1 in 2000 fetuses [83]. Traditionally, open spina bifida was diagnosed via a combination of alpha-fetoprotein from maternal serum or amniocentesis and second-trimester ultrasound evaluations. With the move to first-trimester screening and earlier anatomic ultrasound evaluations, a number of investigators have proposed parameters to assess for these conditions in the first trimester.

Open spina bifida may be accompanied by sonographically visible changes in the posterior fossa at the time of the NT evaluation [84–86]. In these cases, the combination of CSF leakage with a gradual shift of the brainstem towards the occipital bone may result in obliteration of the intracranial translucency or developing fourth ventricle and thickening of the brainstem as it prolapses caudally.

The developing fourth ventricle can be identified as an intracranial translucency (IT) or fluid containing space which is parallel to the nuchal translucency in the midsagittal plane at 11–14 weeks. The IT borders are defined anteriorly by the posterior border of the brain stem and posteriorly by the anterior border choroid plexus (Fig. 7.15). The IT may be absent in cases of open spina bifida and can be assessed between 11 and 14 weeks at the time of NT screening. Initially, it was felt that IT evaluation would be a simple addition to routine NT evaluation given that the structures to be evaluated are in the same plane. However, on further evaluation IT measurement may be more technically challenging than previously thought [87]. It is currently not routine practice in all centers [84–86].

Measurement of the thickness of the brainstem (BS) and the vertical distance between the brainstem anteriorly and occipital bone posteriorly (BSOB) can be obtained between 11 and 14 weeks at the imaging plane at the NT evaluation (Fig. 7.16). The ratio of the BS/BSOB can be

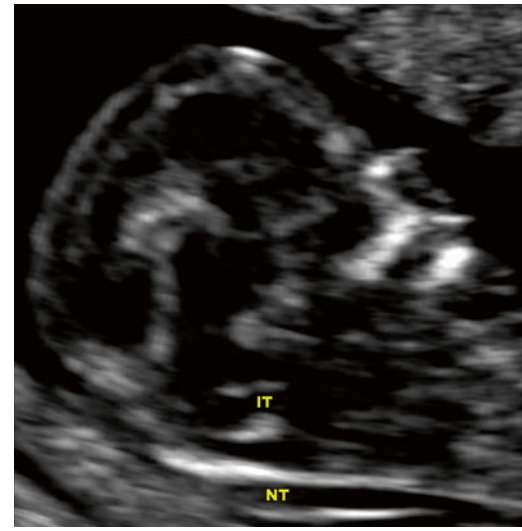

Fig. 7.15 Intracranial translucency. A transabdominal image at 12 weeks, 5 days showing normal intracranial translucency (IT) anterior to the NT. The anterior border of the IT is the brainstem and the posterior border is the choroid plexus

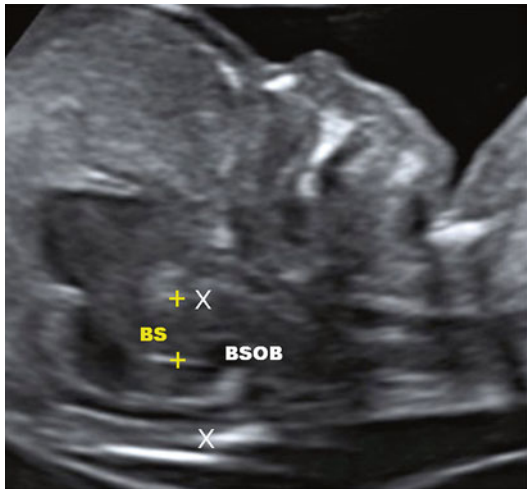

Fig. 7.16 Brainstem to brainstem-occipital bone ratio at 12 weeks, 5 days. Transabdominal image showing the measurement of the brainstem (+) and brainstem to occipital bone distance (*X*)

evaluated and is ≤1 in normal fetuses [86]. In cases of open spina bifida, the BS diameter is greater (>95th percentile) and the BSOB is decreased (<5th percentile) resulting in an increased BS/BSOB ratio > 1 [86, 88]. This is related to the cerebrospinal fluid leakage and development of the Arnold–Chiari II malformation, with a gradual shift of the posterior brain toward the occipital bone. Several studies [84–86] have showed that evaluation of the posterior fossa may be a useful marker for open spina bifida in the first trimester. This is not yet, however, routine practice.

These posterior fossa measurements have proven to be challenging and require a high degree of expertise to perform. More recently it has been demonstrated that the BPD will measure below the 5th percentile in fetuses affected with open spina bifida [89] and may ultimately prove to be the simplest way to assess for coexistent posterior fossa abnormalities associated with the Arnold–Chiari malformation. It is recommended that a targeted ultrasound of the fetus spine, with transvaginal technique, be performed in order to evaluate directly for open spina bifida, in particular when the IT, BS-BSOB ratio, or BPD findings are suspicious or abnormal.

Normal First-Trimester Anatomical Assessment

Formation of most major internal and external organs is complete by the end of the tenth week of gestation during the stage of pregnancy commonly referred to as organogenesis. Assessment of fetal anatomy can, therefore, be attempted in the first trimester, provided that the fetus is large enough to allow visualization of structures with sufficient resolution for diagnostic evaluation, and that organ development be advanced enough that normal developmental stages can be differentiated from pathology. The performance of a first-trimester anatomy scan has become a topic of great interest, as new high frequency transducers, as well as increased use and patient acceptability of transvaginal scanning have enabled better visualization of smaller fetal structures, at earlier gestational ages. It is important, however, to be aware that first-trimester anatomy evaluation is a specialized examination that requires an in-depth understanding of embryology and a high level of technical expertise, particularly with transvaginal techniques and unique scan planes that may be required to visualize some structures. Advantages of first-trimester anatomy assessment include earlier detection of anomalies, earlier patient reassurance in high-risk settings with normal anatomy and potential for better visualization in certain populations, specifically maternal obesity and patients with abdominal scar tissue from prior surgeries. Some disadvantages include increased cost to the medical system, potential to misdiagnose normal developmental structures for pathology and potential to miss diagnoses that do not present until later in pregnancy. Evaluation of first-trimester transvaginal anatomy is generally reserved for high-risk women, including those with elevated NT, inherited conditions associated with fetal anomalies, previous pregnancy with an anomaly, and maternal hazardous exposure or infection.

Several studies have investigated the feasibility and detection rates of performing first-trimester anatomy for anomalies [90–92]. Braithwaite et al. [92] reported that complete

first-trimester anatomic survey was attainable in 95 % of fetuses with transvaginal scanning only required in 20 %. A more recent study of 2876 patients by Ebrashy et al. [93], reported a complete anatomical survey was obtained in 64 % of patients using transabdominal approach only and in 82 % using combination of transabdominal and transvaginal scanning. In their study, transvaginal images were particularly useful to evaluate the cranium, spine, stomach, kidneys, bladder, upper and lower extremities. They reported highest rates of nonvisualization for fetal heart and kidneys. Whitlow and Economides found that visualization of first-trimester anatomy improved with increasing gestational age and reported 98 % visualization at 13 weeks [94]. Monteagudo and Timor-Trisch [95] also support that visualization of first-trimester anatomy, while possible at 12 weeks, is optimally performed closer to 13 weeks. A systematic approach should be used, keeping in mind that some structures seen at the 18- to 22-week scan may not be fully developed in the first trimester. Various protocols have been suggested with respect to what should be included in first-trimester anatomy assessment [96]. Detection rate of anomalies at first-trimester scanning between 11 and 14 weeks has been reported as between 18 % and 68 % [93]. It is important to note that performing a complete first-trimester anatomical survey does not obviate the need for routine anatomical assessment at the 18- to 22-week stage, as some conditions may not develop or be detectable until later in gestation. Nonetheless, in one of the largest prospective studies, including over 45,000 NT evaluations, Syngelaki et al. concluded that certain abnormalities should always be detected during this time period. Specifically they recommended the following conditions should not be missed during a routine NT evaluation: acrania or exencephaly, alobar holoprosencephaly, omphalocele, gastroschisis, megacystis, and body stalk anomaly [97].

In 2012 ISUOG published practice guidelines for first trimester stating that the purpose of the study also includes the detection of gross fetal malformations [2]. The 2013 guidelines from the AIUM state "embryonic/fetal anatomy appropriate for the first trimester should be assessed" [5]. As the 11- to 14-week ultrasound becomes routine practice in more and more centers, it will become more important for ultrasound practitioners to familiarize themselves with the normal embryology and development of the fetus in the first trimester in order to distinguish normal anatomy from pathology at progressive gestational ages.

Fetal Brain in the First Trimester

Early brain development begins in the sixth week of gestation before formation of the neural tube, with division of the neural groove into three distinct parts: the prosencephalon or *forebrain*, the mesencephalon or *midbrain* and the rhombencephalon or *hindbrain*. One of the earliest structures to be visualized, at around 7 weeks, is the rhombencephalon. This appears as a cystic area in the posterior brain which should not be mistaken for pathology such as a posterior fossa cyst (Fig. 7.17). At 8–9 weeks gestation, the choroid plexus begins to develop, initially in the fourth ventricle and, subsequently, in the lateral ventricles. At this stage, the cerebral hemispheres can be delineated, as well as the diencephalon and rhombencephalon. The telencephalon and diencephalon are divisions of the forebrain and give rise to the lateral ventricles and third ventricle, respectively. The metencephalon and myelencephalon are formed from the rhombencephalon. With new high-frequency 2D and 3D transvaginal technology, detailed images of the developing fetal brain and ventricular system can be obtained in the first trimester including images depicting the primary brain structures including the telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon (Fig. 7.18). The lateral ventricles initially appear as small cystic structures and become more identifiable towards the end of the first trimester, when they are filled by the echogenic choroid plexuses. At 9–10 weeks of gestation, the falx cerebri first becomes apparent and cranial ossification begins. These structures are more readily identifiable, however,

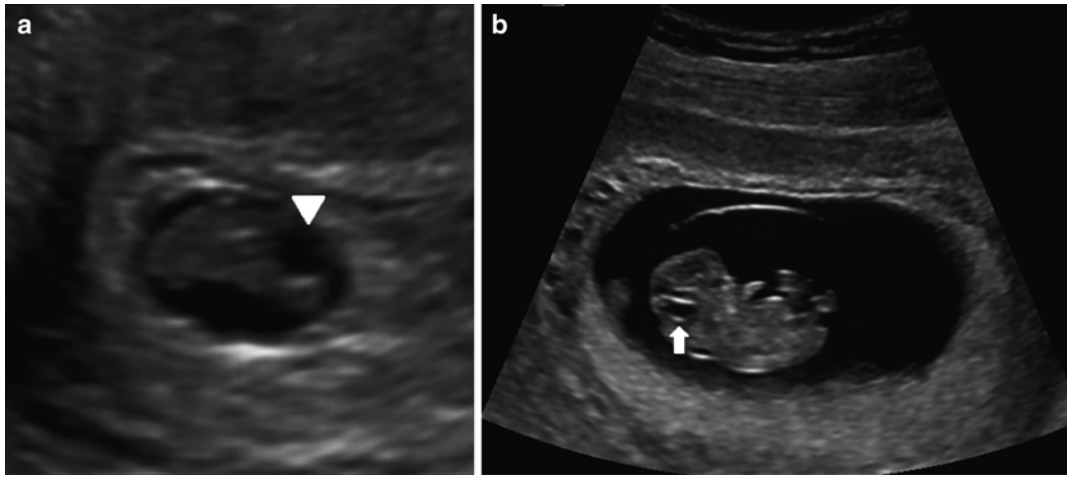

Fig. 7.17 Rhombencephalon. (**a**) Transvaginal image at 7 weeks, 4 days showing cystic rhombencephalon in posterior head (*arrowhead*). (**b**) Transabdominal image at 9 weeks 4 days showing cystic rhombencephalon in posterior head (*arrow*)

closer to 11 weeks gestation and are important landmarks to identify, in order to exclude early diagnosis of anencephaly and alobar holoprosencephaly (Fig. 7.19). Cranial ossification should be seen by the end of the 11th week, is best visualized in the axial and coronal planes in the frontal region and may not be visible in the midsagittal plane, typically used for NT assessment (Fig. 7.20).

The cerebral hemispheres are symmetrical, separated by the interhemispheric fissure and the falx cerebri. The fetal brain has a smooth appearance at this gestation, with sulci and gyri developing later in the second and third trimesters. The cerebral mantle is a thin rim of tissue, seen around the hypoechoic, large lateral ventricles, filled with choroid plexus and occupying most of the cranium at this stage. The posterior fossa structures are not fully developed by the end of the first trimester. The cerebellum and upper vermis can be seen, but the lower vermis is incomplete and persistent communication between the fourth ventricle and cisterna magna is a normal finding at this stage (Fig. 7.21). Structures such as the cavum septum pellucidum and corpus callosum are not yet developed and should be reassessed at a later point in the pregnancy.

Face

Structures that can be assessed include the orbits, lens, profile and nasal bone (Fig. 7.22). The soft tissue structures of the nose and lips are more challenging. Nevertheless, the diagnosis of cleft lip/palate, in particular when bilateral, can be made at this time.

Thorax

The lungs appear as echogenic structures in the developing thoracic cavity and should be symmetric. The diaphragm (black arrow) can be seen as an intact structure separating the echogenic lungs from intra-abdominal contents, specifically the stomach and liver (Fig. 7.23).

Fetal Heart in the First Trimester[4]

Development of the fetal heart begins during the 4th week of gestation and the beating heart can be detected sonographically as early as 5 weeks. Heart position can be documented to confirm

[4] See also Chap. 11.

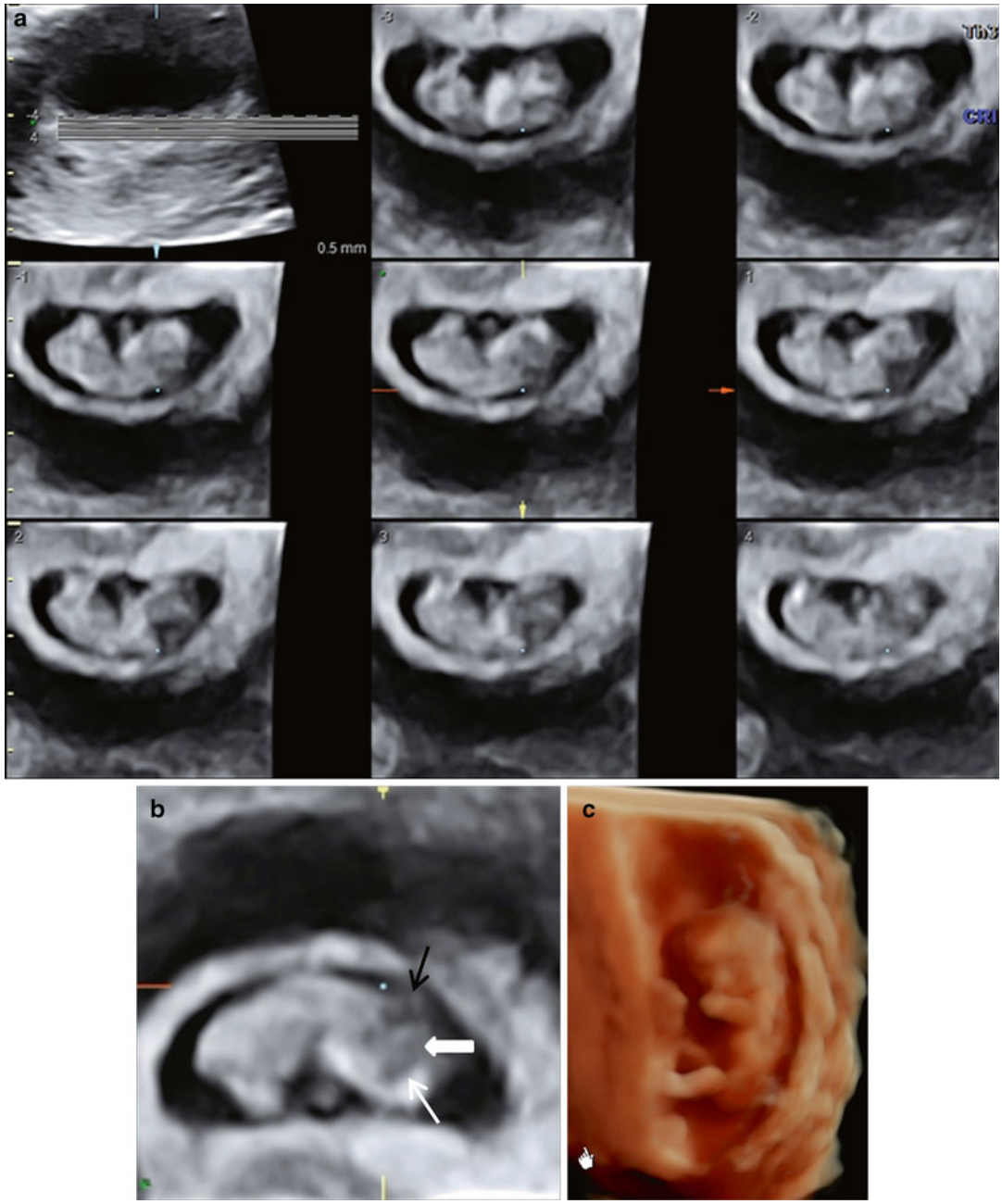

Fig. 7.18 3D brain at 9 weeks, 4 days transabdominal 3D images. (**a**) Serial slicing technique through the 3D volume of the embryo. (**b**) Selected 3D sliced image showing early cystic spaces in the head representing the developing diencephalon (*thin white arrow*), mesencephalon (*thick white arrow*), and metencephalon/myelencephalon (*black arrow*). (**c**) 3D surface rendered image of the embryo

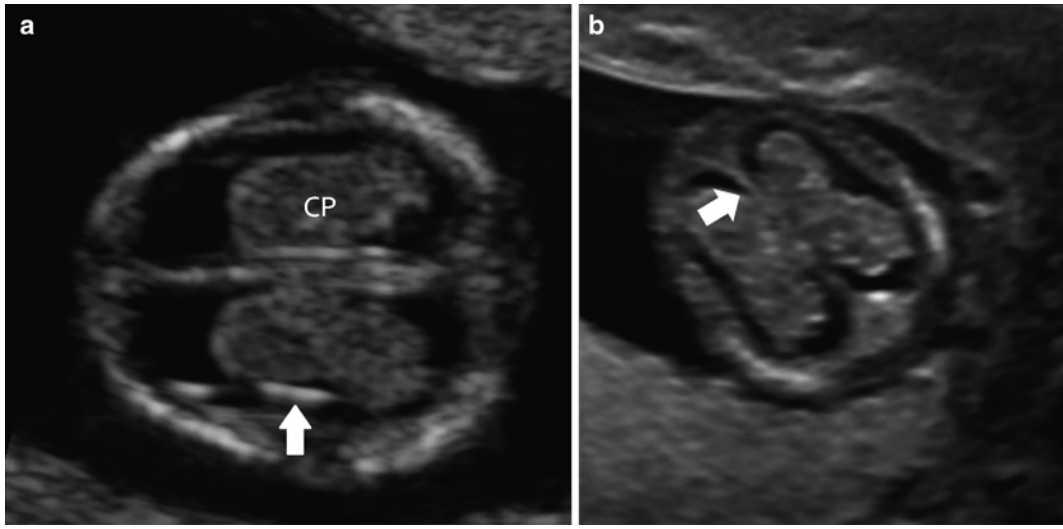

Fig. 7.19 Normal choroid plexus and falx at 12 weeks, 0 days on transabdominal images cranium. (**a**) Bilateral symmetrical echogenic choroid plexuses fill the lateral ventricles. *White arrow* denotes border of lateral ventricle. (**b**) Falx cerebri (*white arrow*) divides the cranium at the level of the choroid plexus resulting in a symmetric appearance of brain. There is only a thin mantle of cerebral tissue at this gestation

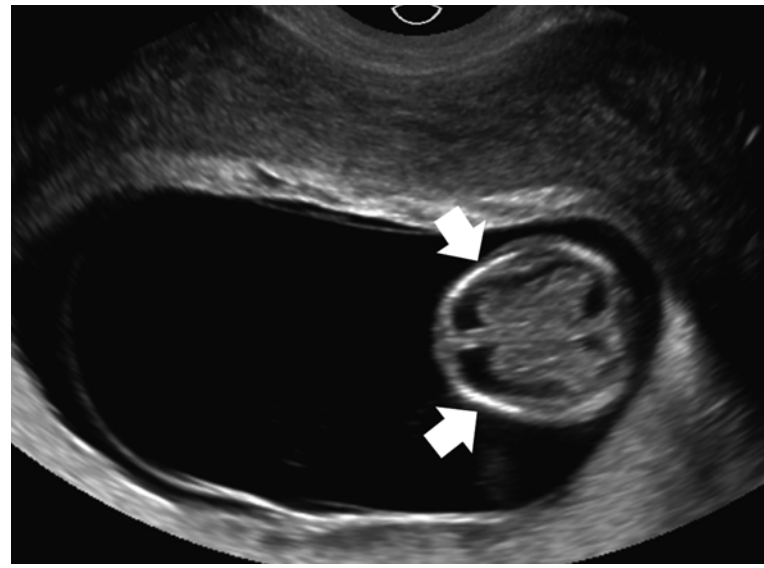

Fig. 7.20 Cranial bone ossification. Transvaginal image at 12 weeks, 3 days of the fetal head showing bilateral normal frontal bone ossification (*white arrows*)

situs solitus. Normal cardiac structures that can be identified during the first trimester include the four-chamber view which should show symmetry of the atria and ventricles with the cardiac apex directed to the left (Fig. 7.24). While the four-chamber view may be seen in as many 85 % of 11 week fetuses, it is visualized in almost all fetuses by the 13th week of gestation [98]. The cardiac outflow tracts are fully developed and may be visible towards the end of the first trimester, although assessment of these structures may be more technically challenging.

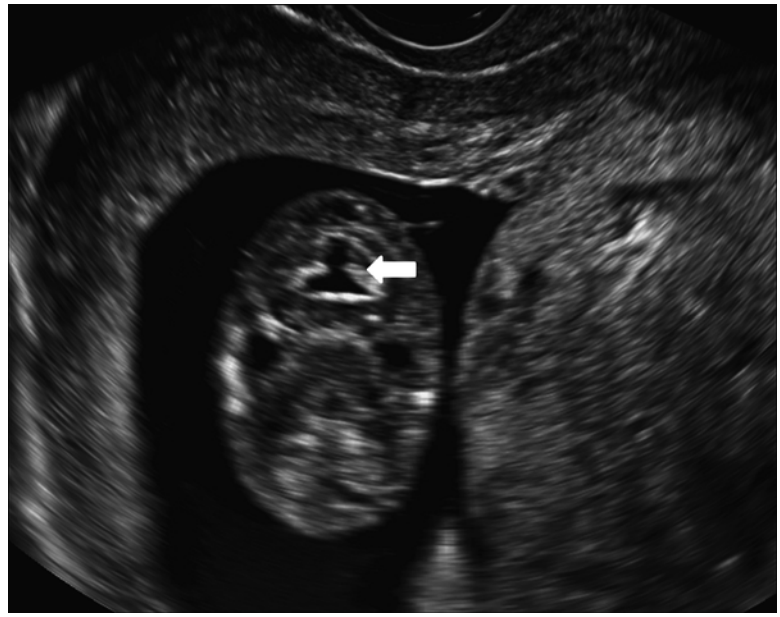

Fig. 7.21 Transvaginal image of posterior fossa at 12 weeks, 3 days showing normal communication of fourth ventricle and cisterna magna (*white arrow*) due to incomplete development of the cerebellar vermis

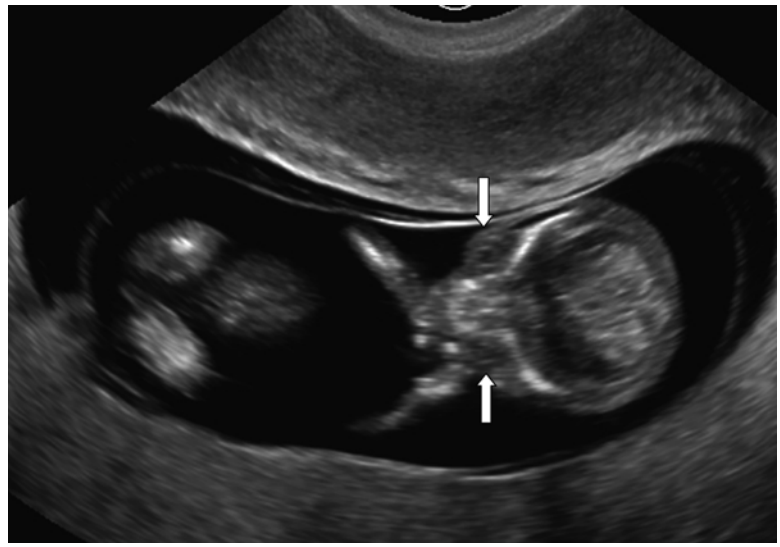

Fig. 7.22 Normal orbits and lenses. Transvaginal semi-coronal image at 12 weeks, 3 days showing normal orbits and lenses (*arrows*)

Fetal Kidneys and Urinary Tract System in the First Trimester

The fetal kidneys are sonographically detectable by the ninth week of gestation. The fetal bladder is not reliably visualized until later in the first trimester at around 12 weeks (Fig. 7.25). By 13 weeks gestation, the bladder can be seen in up to 98 % of cases and kidneys in up to 99 % [99]. Documentation of these structures is important, as urine production does not begin until the 12th or 13th week, and secondary signs of renal agenesis or dysfunction, such as oligohydramnios, may not manifest until later in pregnancy after 16 weeks gestation.

The normal urinary bladder should measure less than 7 mm in midsagittal dimension at the time of the NT evaluation [99]. When it is greater

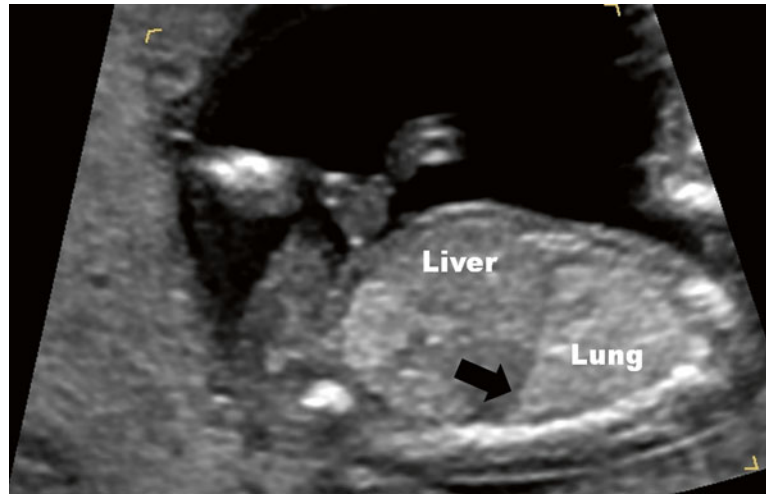

Fig. 7.23 Fetal chest and diaphragm. Transabdominal image at 12 weeks, 2 days showing echogenic fetal lungs separated by intact diaphragm from the more hypoechoic liver

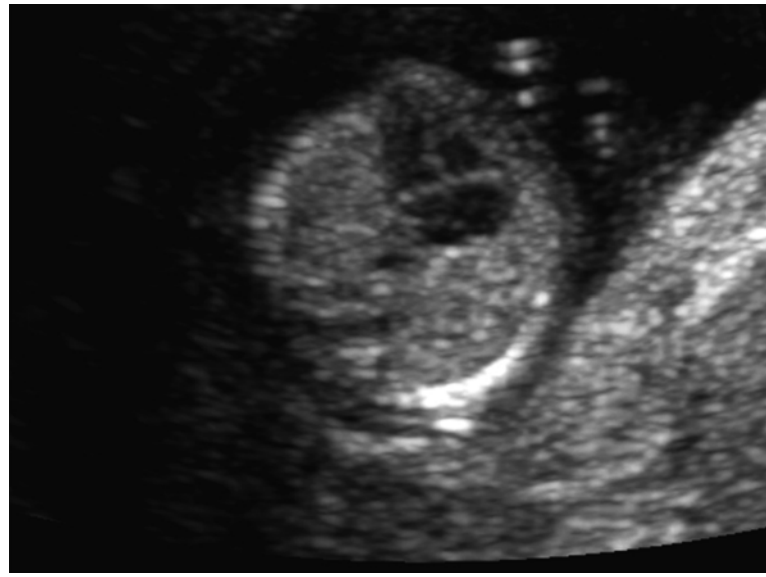

Fig. 7.24 Four-chamber heart. Transabdominal image at 13 weeks showing four-chamber heart

than 16 mm, the majority of fetuses will have a poor outcome. In the 7- to 15-mm range, in the euploid group, the majority (>90 %) will have a normal outcome [100]. It is felt that this euploid group with transient megacystis may be related to a delay in autonomic innervation of the smooth muscle of the bladder wall. An initial follow-up in 2 weeks is a reasonable approach in this intermediate group.

Fetal Gastrointestinal Tract in the First Trimester

In the embryonic period, the midgut herniates into the umbilical cord at the start of the eighth weeks and, following a 90° rotation, returns to the abdominal cavity by the end of the 12th week. Although normal physiological midgut herniation should measure less than 10 mm prior to 10

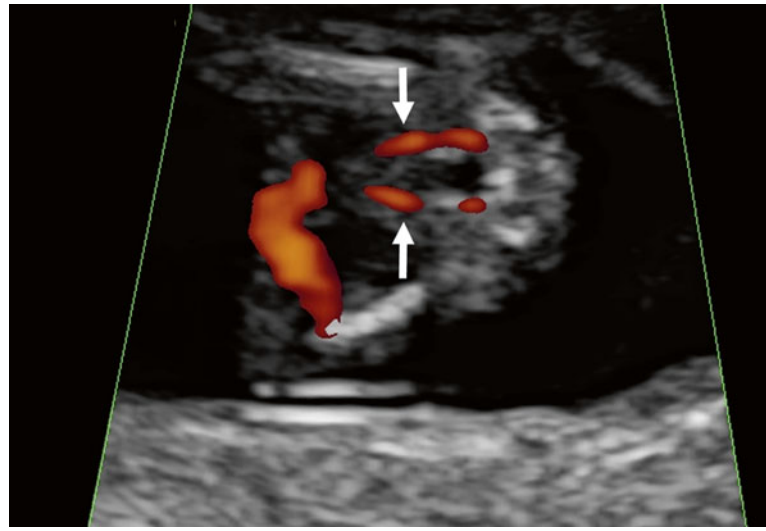

Fig. 7.25 Fetal bladder. Transabdominal image at 12 weeks, 0 days showing fetal bladder with two umbilical arteries coursing adjacent to bladder walls

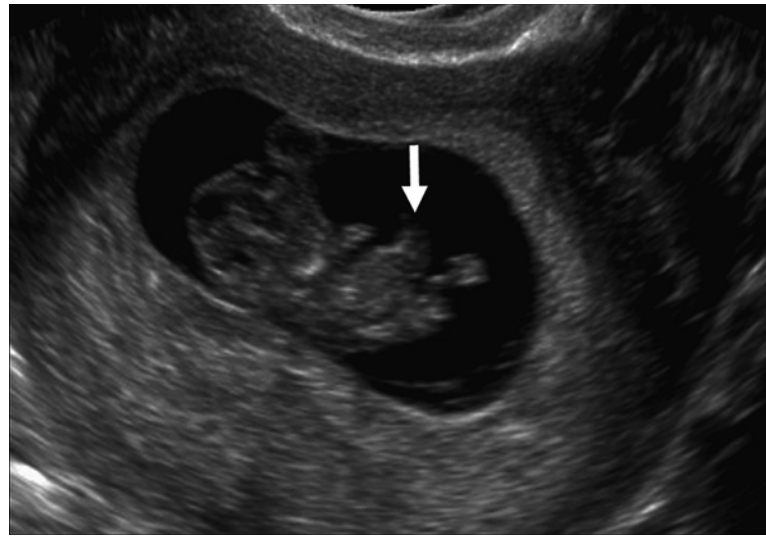

Fig. 7.26 Physiologic midgut herniation. Transvaginal image at 9 weeks, 3 days showing echogenic mass protruding centrally within umbilical cord (*arrow*) representing normal-appearance herniated bowel

weeks and should resolve by 12 weeks, there remains some variability in timing of when the midgut fully returns to the abdomen and herniated bowel may still be present at 12 weeks in up to 20 % of fetuses. If midgut herniation is still suspected at 12 weeks, follow-up imaging is recommended to ensure complete return of the herniated bowel into the abdominal cavity. The normal appearance of herniated bowel is an echogenic mass in the central cord, which progressively decreases in size towards the ninth and tenth week [97] (Fig. 7.26). The liver should never be present within the herniated contents. The fetal stomach can be visualized as a fluid-filled structure in the upper abdomen by 12–13 weeks [92] (Fig. 7.27). Absence of the stomach at sonography may be seen in cases of esophageal atresia; however, serial scans documenting persistent nonvisualization of the stomach are required to make this diagnosis.

Abdominal Wall and Umbilical Cord

Normal cord insertion, centrally within the abdomen, can be routinely documented after 12 weeks, following the return of the small bowel into the abdominal cavity. Number of cord vessels can be assessed and normal appearance of two arteries and one vein can be seen, either on grey scale in cross-section, or by using color Doppler to show two arteries adjacent to the urinary bladder (see Fig. 7.25). Umbilical cord cysts can be seen and may be associated with chromosomal abnormalities. However, these can also be a normal variant and may resolve on subsequent imaging.

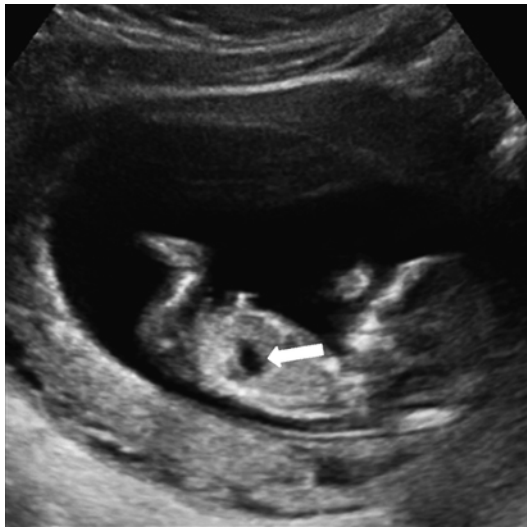

Fig. 7.27 Fetal stomach. Transabdominal image at 12 weeks showing fluid-filled stomach (*arrow*) below the diaphragm

Fetal Skeleton in the First Trimester

Limb buds start to form as early as the fourth week of gestation. They are first identified at ultrasound, however, between 8 and 9 weeks gestation. Ossification of the long bones of the skeletal system can be seen at around 10 weeks. Distal ossification of the phalanges is present by 11 weeks gestation. It is important to document the presence of four limbs, with each limb demonstrating three segments (Fig. 7.28). In normal development, the ratio between upper extremity and lower extremity long bones should approximate 1.0. Disproportionate length of either upper or lower extremities can indicate an underlying skeletal dysplasia and warrants further assessment. Biometry of long bones can be performed with accuracy after 11 weeks and published normograms are available for reference [101].

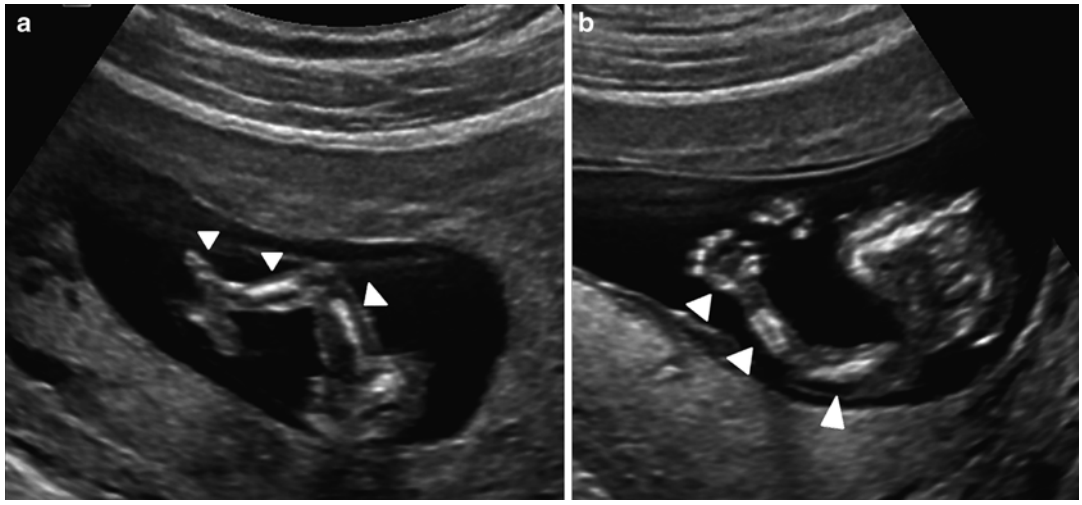

Fig. 7.28 (**a**) Transabdominal image at 12 weeks showing three segments of lower extremity (*arrowheads*). (**b**) Transabdominal image showing three segments of upper extremity (*arrowheads*). Note the ossified individual digits of the hand can be distinctly seen

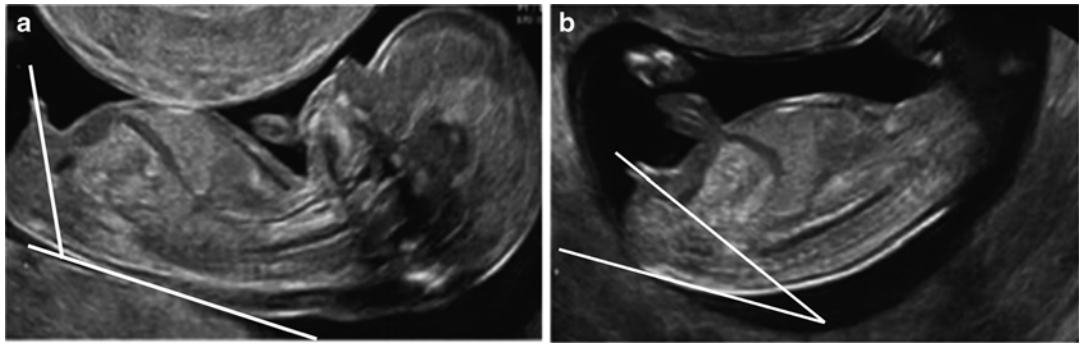

Fig. 7.29 Transvaginal images of genital tubercle at 12 weeks. (**a**) Vertical orientation of genital tubercle (>30° angulation) in male fetus. (**b**) More horizontal angle of genital tubercle (<10°) in female fetus

Assessment of Fetal Genitalia in the First Trimester

In early pregnancy the genital tubercle is identical in size in male and female fetuses. Accurate sonographic sex determination, based on external genitalia can be performed between 12 and 14 weeks [102]. Gender determination at this stage is based upon orientation of the genital tubercle, as seen in the midsagittal plane. The angle of the genital tubercle to a horizontal line through the lumbosacral skin surface is measured. Male gender is assigned if the angle is greater than 30° and female gender if the angle is less than 10° (Fig. 7.29). Gender assignment is considered indeterminate if the angle is between 10° and 30°. Accuracy of gender assignment in higher in male fetuses and accuracy increases with increasing gestational age, with near 100 % reliable gender identification possible at 13+6 weeks. Early assignment of fetal gender may be useful in decision-making with regards to invasive testing, such as CVS, in patients at increased risk of sex-linked disorders [103]. It should be noted that fetal sex determination using cell-free fetal DNA in maternal plasma is increasingly performed in pregnancies at increased risk of X-linked genetic disorders or congenital adrenal hyperplasia. Early reporting of fetal gender is controversial as it may facilitate the practice of sex selection.

Assessment of Spine

Longitudinal and axial views can demonstrate normal alignment and integrity of the overlying skin, in particular towards the end of first trimester. Detailed spine assessment is recommended when the BPD measurements are less than the 5th percentile or a posterior fossa abnormality is suspected [89].

Role of Three-Dimensional (3D) and Four-Dimensional (4D) Ultrasound

Three-dimensional and 4D ultrasound are not part of the routine first-trimester care evaluation. Their role remains an area for further research.[5]

Summary

In summary, the main goal of a first trimester ultrasound is to provide information which can be used to optimize antenatal care. The establishment of a viable intrauterine pregnancy, accurate dating and assessment of the fetal number, chorionicity, and amnionicity are crucial components

[5] See also Chap. 13.

of an early pregnancy evaluation. Evaluation of the nuchal translucency is now routine practice in many centers and, when combined with maternal serology, is useful in assessing aneuploidy risk. Transvaginal ultrasound provides an opportunity for a detailed anatomic evaluation of the developing embryo and fetus and potential earlier detection of anomalies in the first trimester. It is, therefore, increasingly important to be familiar with the developmental stages of the embryo and fetus at various stages in the first trimester.

Teaching Points

- Without sonographic evidence of ectopic pregnancy, any fluid collection with curved margins in a woman with a positive pregnancy test should be considered an early intrauterine gestational sac.
- The most accurate sonographic sign for confirmation of an IUP is visualization of the yolk sac.
- An empty gestational sac should be considered a potentially normal early pregnancy finding up to an MSD of 25 mm on transvaginal ultrasound.
- The absence of embryonic cardiac activity should be considered a potentially normal finding up to a measured embryo length of 7 mm.
- Assignment of chorionicity is a mandatory and vital component of first-trimester ultrasound with multiple gestations.
- The most accurate estimation of gestational age is achieved in the first trimester by using the CRL between 8 weeks and 13 + 6 weeks.
- Assessment of nuchal translucency, especially when combined with maternal age and maternal serum biochemistry, can be an effective method of screening for chromosomal abnormalities.
- In euploid fetuses borderline or mild elevated nuchal translucency may be associated with a normal outcome.
- It is important for practitioners to be familiar with normal anatomy at various gestational ages in the first trimester.

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Aneuploidy Screening: The Ongoing Role of First-Trimester Ultrasound

8

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Introduction

The concept of prenatal screening for aneuploidy began with the discovery that fetal Down syndrome risk correlated with maternal age [1]. Maternal serum screening (MSS) utilizing feto-placental proteins was developed in an attempt to provide more pregnancy specific risk assessment [2]. While studying increased maternal serum alpha-fetoprotein for the detection of open neural tube defects it was also noted that this marker was decreased in pregnancies with Down syndrome [3]. Other markers including, human chorionic gonadotropin, unconjugated estriol, and dimeric inhibin A, were then also found to display a characteristic pattern in pregnancies with Down syndrome leading to the development of second-trimester double, triple, and quadruple screening, respectively [4]. The accuracy of these maternal serum screens is heavily dependent on the clinical information entered into the algorithm. Incorporation of just one incorrect parameter (i.e., gestational age) can provide a false-positive or false-negative result. An additional drawback to these screens is the delay in performance until the second trimester, excluding the option for early termination in the case of an affected pregnancy.

First-trimester screening including incorporation of fetal nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), and the beta subunit of human chorionic gonadotropin (β-hCG), soon emerged as a superior screening method [5]. This approach eliminates the error due to inaccurate gestational dating, since ultrasound measurement of the fetal crown-rump length is part of the algorithm. First-trimester screening achieves a high detection rate for Down syndrome (85 %–90 %) and trisomy 18 (90 %–95 %) with a 5 % false-positive rate, and provides earlier prenatal diagnosis and the option of termination in the case of an affected pregnancy [6, 7].

Several screening modalities that incorporate elements in both the first and second trimesters were then created to further increase the detection rate and decrease the false-positive rate. There are various strategies to performing this type of combined screening, including those which incorporate only serum feto-placental

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protein markers (i.e., serum integrated) as well as those incorporating ultrasound and serum markers (i.e., integrated, sequential, and contingent) [8]. The type of strategy utilized depends on patient preference as well as availability of certified NT providers.

Second-trimester ultrasound for evaluation of structural malformations and "soft markers" is also utilized as a screening for fetal aneuploidy. Some centers will perform "genetic sonograms" by incorporating likelihood ratios for various ultrasound markers to produce a risk for aneuploidy, mainly Down syndrome. This information is often interpreted in the context of the patient's other risk factors, including age and MSS results. There is a wealth of literature regarding the utility of second-trimester ultrasound screening for aneuploidy, which is outside the scope of this chapter [9–12].

In 1997 Lo et al. first discovered circulating cell-free fetal DNA (ccffDNA) in the plasma of pregnant women initiating efforts to create a reliable noninvasive method for detecting fetal aneuploidy [13]. More than a decade later massively parallel sequencing (MPS) of cell free fetal DNA was shown to detect an overrepresentation of chromosome 21 material in pregnancies affected with trisomy 21 [14, 15]. This led to a number of clinical trials validating MPS as a highly sensitive and specific noninvasive tool to detect common chromosomal aneuploidies [16–18] in a high-risk patient population. This technology became clinically available in late 2011 and has significantly shifted the paradigm of prenatal screening and diagnosis in many centers throughout the world and resulted in a decrease in the number of invasive procedures performed for aneuploidy testing [19]. Screening for aneuploidy through cell free fetal DNA analysis has caused us to reevaluate the way we think of screening, even in low-risk populations [20]. The traditional definition of screening, in which the majority of individuals with a positive result do not have the disease of interest, which is true of standard maternal serum screen modalities, does not apply because of the high positive predictive value of the results [21].

Biochemical and Ultrasound Screening for Aneuploidy

Historical Approaches

As early as the 1960s, maternal age was recognized as a risk factor for fetal aneuploidy. Rates of chromosome abnormalities at different maternal ages (Table 8.1) were published in the 1980s to aid genetic counseling for these conditions, especially given the uptake in prenatal diagnosis due to improved safety and efficacy of invasive prenatal diagnosis [1, 22].

Historically, women over 35 years of age at term were considered "high risk" for chromosome aneuploidy and were offered invasive prenatal diagnosis via fetal karyotyping following amniocentesis or chorionic villus sampling. Age 35 was selected as the cut-off, in part, due to the often-quoted 1 in 200 risk of complications with amniocentesis; the risk of aneuploidy was felt to be approximately equal to or greater than the procedural risk. The cost-effectiveness and utility of this approach was questioned, particularly in light of the procedure-related pregnancy loss rate [23].

Second-Trimester Maternal Serum Biochemical Screening

Second-trimester biochemical maternal serum screening started with the finding that low maternal serum alpha-fetoprotein (MS-AFP) was associated with an increased risk of Down syndrome [3]. Maternal serum screening for aneuploidy then expanded to include multiple additional markers: hCG, unconjugated estriol (uE3), dimeric inhibin A (DIA), and in some laboratories, invasive trophoblast antigen (ITA) [4]. These quadruple ("Quad") or "Penta" screens provided additional parameters by which to estimate a woman's risk of fetal aneuploidy in a given pregnancy, with higher sensitivity than age alone (approximately 80 % for Down syndrome at a 5 % false-positive rate). The "pattern" of high or low levels (as calculated by MoM) of these

Table 8.1 Estimates of rates of chromosome abnormalities in live-born infants[a]

Age of mother at term (years)	Risk for trisomy 21 (Down syndrome) (%)		Total risk for any chromosome abnormality[b] (%)	
20[c]	1/1667	0.06	1/526	0.2
21	1/1429	0.07	1/526	0.2
22	1/1429	0.07	1/500	0.2
23	1/1429	0.07	1/500	0.2
24	1/1250	0.08	1/476	0.2
25	1/1250	0.08	1/476	0.2
26	1/1176	0.09	1/476	0.2
27	1/1111	0.09	1/455	0.2
28	1/1053	0.09	1/435	0.2
29	1/1000	0.10	1/417	0.2
30	1/952	0.11	1/384	0.3
31	1/909	0.11	1/384	0.3
32	1/769	0.13	1/323	0.3
33	1/625	0.16	1/286	0.3
34	1/500	0.20	1/238	0.4
35	1/385	0.26	1/192	0.5
36	1/294	0.34	1/156	0.6
37	1/227	0.44	1/127	0.8
38	1/175	0.57	1/102	1.0
39	1/137	0.73	1/83	1.2
40	1/106	0.94	1/66	1.5
41	1/82	1.2	1/53	1.9
42	1/64	1.6	1/42	2.4
43	1/50	2.0	1/33	3.0
44	1/38	2.6	1/26	3.8
45	1/30	3.3	1/21	4.8
46	1/23	4.3	1/16	6.3
47	1/18	5.6	1/13	7.7
48	1/14	7.1	1/10	10.0
49	1/11	9.1	1/8	12.5

[a]Adapted from Hook 1981 and Hook et al. 1983
[b]Includes trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), and sex chromosome aneuploidies (XYY and XXY). Monosomy X (Turner syndrome) is excluded as it is not significantly correlated to maternal age. Trisomy X (XXX) is excluded as the clinical significance of this aneuploidy was in question at time of calculation of these estimates
[c]No risk range may be constructed for women less than 20 years [1, 22]

analytes, combined with maternal age, weight, gestational age (ideally confirmed by ultrasound biometry), and race are used to calculate risk for fetal Down syndrome, trisomy 18, and ONTD; see Table 8.2 for a summary. In some centers, a risk for Smith–Lemli–Opitz syndrome (SLOS, an autosomal recessive condition characterized by a range of intellectual disability, growth restriction, and structural anomalies) is also calculated based on low serum estriol. Although no uniformly accepted practice exists, it has been suggested in multiple studies that unexplained extreme values of second-trimester analytes should prompt further investigation and increased maternal-fetal monitoring [24, 25].

First-Trimester Maternal Serum Biochemical Screening

In an effort to perform risk assessment for aneuploidy at an earlier gestational age, first-trimester markers for aneuploidy were investigated. Previously used second-trimester markers were explored for utility in the first trimester, but only hCG was found to be informative; elevated hCG is associated with an increased risk for Down syndrome. PAPP-A, another product of the placenta, is found in low levels in maternal serum of affected pregnancies. Low levels of both analytes are concerning for trisomy 18. Taken together, these two markers had a 65 % detection rate at a 5 % false-positive rate for Down syndrome; however, second-trimester maternal serum screening had a higher detection rate. Therefore, additional markers were needed to improve first-trimester screening [5].

First-Trimester Ultrasound Markers for Chromosomal and Genetic Anomalies

Nuchal translucency (NT), a measurement of the thickness of the subcutaneous fluid at the back of the neck of the fetus in the late first trimester, was observed to be increased in fetuses with Down syndrome. Stringent, efficacious and standardized methods for measurement of the fetal NT were developed in the early 1990s [28]. NT alone was found to have a ~75 % detection rate and ~5 % false-positive rate for Down syndrome [29]. Kagan and colleagues found that 19.2 % of

Table 8.2 Patterns of second-trimester maternal serum analytes and risk assessment for screened conditions [24–26]

Analyte	Trisomy 21	Trisomy 18	ONTD	Other risks with high levels (>2.0 MoM)	Other risks with low levels (<0.5 MoM)
MS-AFP	↓	↓	↑	Birth defects (not limited to ONTD or OAWD), fetal death, placental abnormality, IUGR, fetal distress	Fetal death, preterm birth[a]
hCG	↑	↓	–	Birth defects (not limited to trisomy 21), IUGR, fetal distress[b]	IUGR, birth defects[b]
uE3	↓	↓	–	No significant risks	IUGR, fetal death; certain single-gene conditions (X-linked ichthyosis, congenital adrenal hyperplasia)
DIA	↑	↓	–	Preeclampsia, fetal death, preterm birth, IUGR	No significant risks

Abbreviations: IUGR, intrauterine growth restriction (birth weight <10th percentile for gestational age) [25]; OAWD, open abdominal wall defects; ONTD, open neural tube defects
[a]MS-AFP levels considered low at <0.25 MoM [27]
[b]hCG levels considered high at >2.5 MoM and low at <0.4 MoM [25]

pregnancies with NT >3.4 mm had an abnormal karyotype [30]. Furthermore, the incidence of chromosomal defects increased with NT thickness, from approximately 7 % with an NT of 3.4 mm (95th percentile for crown-rump length) to 75 % for an NT of ≥8.5 mm. The majority of fetuses with Down syndrome had an NT of <4.5 mm, whereas in the majority of fetuses with trisomies 13 or 18, NT measurement was 4.5 to 8.4 mm. Fetuses with Turner syndrome tended to have an NT of 8.5 mm or more (Table 8.3).

While the risk of numerical chromosome anomalies can be clarified by fetal karyotype, microdeletion and microduplication syndromes have been increasingly associated with thickened fetal NT. Chromosomal microarray (CMA, also called array comparative genomic hybridization or array CGH) can interrogate fetal DNA obtained by CVS or amniocentesis and detect small (~1–3 megabases [Mb]) genome-wide deletions or duplications of DNA (copy number variations [CNVs]). This is performed by comparing fetal DNA against a reference genome via a microchip-based reaction. For additional information about this tool, the reader is referred to ACOG Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis [52].

In a 2015 study by Lund and colleagues, in fetuses with isolated NT ≥3.5 mm, clinically significant CNVs were detected in 12.8 % of cases with normal karyotype; an additional 3.2 % had CNVs of uncertain clinical significance [53]. Clinically significant CNVs were detected in 14.3 % of fetuses with an NT of 3.5 to 4 mm, structural anomalies in other systems, and a normal karyotype; detection rate was 16.7 % in similar cases where NT measured ≥4 mm [54]. Notably, chromosomal microarray can detect 22q11.2 deletion syndrome, the CNV most commonly associated with increased NT and cardiac defects (see Table 8.3).

It should be noted that, while the clinical significance of thousands of pathologic and benign CNVs has been well documented, there remain regions of the genome for which the significance of a microduplication or microdeletion is not known. Furthermore, chromosomal microarray may incidentally detect consanguinity (including incest), non-paternity, and genetic abnormalities associated with adult-onset disorders that may be inherited from an asymptomatic parent.

Table 8.3 Common genetic conditions associated with increased first-trimester nuchal translucency [31–33]

Syndrome	Incidence (% of fetuses with increased NT)	Etiology	Inheritance	Features	Testing considerations
Turner syndrome (Monosomy X)	1 in 2000 females (~6.7 %; associated with larger NTs compared to Down syndrome. Highest incidence (12.3 %) if NT is 5.5–6.5 mm [30]	Presence of a 45,X cell line	Sporadic	Prenatal: cardiac defects and cystic hygroma (resulting in a webbed neck in the postnatal period); associated high risk of IUFD Postnatal: short stature, cardiac and kidney malformations, webbed neck, lymphedema, reduced fertility, and risk for mild developmental and learning delays [35]	May be diagnosed incidental to prenatal screening or testing for fetal trisomy. Low-level mosaicism may be undetectable by standard fetal karyotype and chromosome microarray. FISH[a] of additional interphase cells may improve detection and identify Y chromosome material, which confers a risk of postnatal gonadoblastoma [34]
Noonan syndrome	1 in 1000–2500 (2–5 %) [36, 37]	Mutation in genes encoding proteins in Ras/MAPK signaling pathway (most commonly *PTPN11*, but also *SOS1*, *RAF1*, *BRAF*, *MAP2K1*, *MAP2K2*, *NRAS*, *SHOC2*, *CBL*, *HRAS*, and *KRAS*) [38]	Autosomal dominant; de novo in 25–70 % of cases [39]	Prenatal: hydrops fetalis, cardiac anomalies; polyhydramnios, bilateral pyelectasis and ventriculomegaly have been reported [40] Postnatal: wide variability; short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, pectus, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Apparently asymptomatic individuals exist. Part of a spectrum of disorders (including Leopard syndrome, cardiofaciocutaneous (CFC) syndrome, and Costello syndrome) [38]	Prenatal molecular genetic diagnosis on chorionic villi or amniocytes via a panel of genes is clinically available, though detection rate is only ~70 % [33]

(continued)

Table 8.3 (continued)

Syndrome	Incidence (% of fetuses with increased NT)	Etiology	Inheritance	Features	Testing considerations
22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome [VCFS])	1 in 4000 (~3 % if prenatal heart defects noted [41]	Microdeletion of chromosome 22 at band q11.2; size of deletion may vary	Autosomal dominant; de novo in ~90 % of cases [42, 43]	Prenatal: conotruncal heart defects; hypoplastic/absent thymus, bilateral club feet, and renal cystic dysplasia have also been reported [44, 45]	Prenatal testing (FISH or chromosome microarray) for 22q11.2 deletions may be considered in fetuses with congenital heart defects and concomitant increased NT; the value of routine testing in the absence of heart defects is not clear [36, 46–48]
				Postnatal: conotruncal heart defects, neonatal hypocalcemia, hypothyroidism, palatal defects, immune deficiency, short stature, gastrointestinal, genitourinary and ophthalmologic disease; normal IQ to mild intellectual disability, autism spectrum disorder, increased risk for psychiatric disorders in adulthood [43]	
Skeletal dysplasias	Estimated at ~1 in 2200 to 4400 live births [49]	Heterogeneous group of genetic conditions	May be autosomal dominant, autosomal recessive or X-linked; many de novo [49]	Prenatal: hydrops, short femurs, abnormal skull shape and mineralization, abnormal profile, abnormal chest. Second-trimester anatomy scan may reveal additional findings. Risk of IUFD, particularly where chest anomalies increase likelihood of pulmonary insufficiency. Some not compatible with long-term survival [49]	Given the large number of genes associated with skeletal anomalies, gene "panels" that simultaneously test multiple genes may assist in determining the correct diagnosis and the recurrence risk of the condition for future pregnancies [33, 50]. If possible, postnatal evaluation by a pediatric geneticist may be beneficial in establishing a diagnosis
				Postnatal: short stature, limb shortening; varies greatly depending on the underlying diagnosis	

[a]FISH, or fluorescent in-situ hybridization, a method for rapid enumeration of chromosomes 21, 13, 18, X and Y on uncultured chorionic villi and amniocytes. For additional information, please refer to the 2001 review by Tepperberg and colleagues [51]

Therefore, it is recommended that genetic counseling with informed consent be obtained prior to performing microarray in cases with increased fetal NT [52].

In the event that fetal chromosome abnormality has been ruled out, an increased NT may be indicative of many other genetic and nongenetic conditions. Of the single gene conditions, the most common is Noonan syndrome (see Table 8.3). A link between increased NT and several other single-gene conditions and have been suggested. However, due to the rarity of most of these conditions (most have an incidence of <1 in 10,000), a definitive association between increased NT and these conditions cannot be statistically proven. Furthermore, the single-gene and often *de novo* molecular cause of these conditions is not amenable to comprehensive prenatal genetic diagnosis [31, 32]. As can be surmised from Table 8.3, many conditions have sonographically diagnosable fetal anomalies, in addition to an increased NT, albeit, not always in the first or early second trimesters.

In addition to nuchal translucency, evaluation of the fetal nasal bone is a benefit of first-trimester ultrasound. Hypoplastic or absent nasal bone has been associated with fetal Down syndrome. Nasal bone evaluation between 11 0/7 to 13 6/7 weeks is included in first-trimester screening for Down syndrome in some centers, as it is independent of other first-trimester markers (free β-hCG, PAPP-A, and NT). In one series, the nasal bone was absent in 2.6 % of the euploid fetuses (though this may vary with ethnicity); it was absent in 59.8 % of the fetuses with trisomy 21, 52.8 % with trisomy 18, 45.0 % with trisomy 13 and in none of the fetuses with Turner syndrome [55]. At a false-positive rate of 5 %, nasal bone evaluation in addition to NT and serum analytes was estimated to achieve a sensitivity of >95 % for trisomy 21, 18 and 13, and is not thought to significantly prolong ultrasound examination time [55, 56]. Much like nuchal translucency, rigorous guidelines have been established for measurement of this feature, which is outside the scope of this chapter (see Chap. 9).

More recently, first-trimester evaluation of flow in the ductus venosus and across the tricuspid valve via Doppler has been proposed to aid in risk assessment and improve detection rate for fetal aneuploidy. In one prospective study, a ductus venosus pulsatility index for veins (DV-PIV) demonstrating a reversed a-wave was estimated to detect 96 %, 92 %, 100 %, and 100 % of trisomies 21, 18, and 13 and Turner syndrome, respectively, at a false-positive rate of 3 %, when combined with maternal age, NT, fetal heart rate, and β-hCH and PAPP-A [57]. In the same cohort of patients, assessment of tricuspid flow for regurgitation demonstrated the same detection rates for chromosomal anomalies as DV-PIV [58].

Benefits of First-Trimester Ultrasound in Detection of Non-chromosomal Fetal Anomalies

Despite increased utilization of noninvasive DNA screening (NIDS) for fetal aneuploidy, first-trimester ultrasound remains a useful screening tool for non-chromosomal conditions that may have a significant impact on prenatal and postnatal outcome. Increased NT is a risk factor for fetal congenital heart defects (CHD), although no pattern of specific CHD has been described. An NT >95th percentile for crown-rump length has been associated with a significantly increased risk for CHD in fetuses with a normal karyotype, with a detection rate for major CHD of ~44 % for a 5.5 % false-positive rate [59]. Doppler evaluation of the tricuspid valve and ductus venosus at first-trimester ultrasound can also improve the detection rate; 32.9 % of euploid fetuses with major CHD had tricuspid valve regurgitation, and 28 % had an abnormal a-wave in the ductus venosus (compared to 1.3 % and 2.1 % of those without CHD, respectively) [60]. The current consensus is that fetal echocardiogram, performed as early as the late first trimester, should be considered in pregnancies with increased NT (>3.5 mm), particularly as some studies have showed improved neonatal outcome in ductal dependent

CHD after being identified via NT measurement [31, 61, 62]. Additional discussion on first-trimester detection of CHD is found in Chap. 11.

First-trimester increased NT has also been associated with fetal death, with risk appearing to directly correlate with NT measurement; overall risk is ~4 %, ranging from ~2 % at 3.5 mm to ~17 % at >6.5 mm [33, 63]. It may be an early indicator of structural anomalies, including but not limited to body stalk anomaly, diaphragmatic hernia, omphalocele, orofacial clefts, fetal akinesia sequence and megacystis. The overall incidence of structural anomaly with NT >3.5 mm is estimated at ~12 % in the presence of a normal fetal karyotype [32, 33, 63]. Fetal infection is often cited as a possible cause for increased NT. Parvovirus B19 infection is the only specific pathogen associated with increased NT, most likely secondary to myocardial dysfunction or fetal anemia [64].

In twin gestations, first-trimester markers (including NT, nasal bone, tricuspid valve flow, and DV-PIV) may be helpful in risk assessment for aneuploidy as they are independent measurements for each fetus, regardless of chorionicity; however, NT is also helpful in assessing risk of twin-to-twin transfusion syndrome for monochorionic twins [65].

Current Methods of First-Trimester Maternal Serum Aneuploidy Screening

In 2007, the American College of Obstetrics and Gynecology published a practice bulletin stating that "first-trimester screening using both nuchal translucency measurement and biochemical markers is an effective screening test for Down syndrome in the general population… Screening and invasive diagnostic testing for aneuploidy should be available to all women who present for prenatal care before 20 weeks of gestation regardless of maternal age"[4].

There are many current screening methodologies to address these recommendations, using different combinations of first-trimester ultrasound, first-trimester biochemical markers, and second-trimester biochemical markers to generate a risk assessment for aneuploidy. First-trimester analyte screening uses PAPP-A and hCG analytes; first-trimester combined screening adds nuchal translucency with or without nasal bone measurement. Similarly, integrated and serum integrated screening combine first-trimester PAPP-A measurement with second-trimester analytes, with our without first-trimester ultrasound parameters, respectively. Stepwise sequential and contingency screening allow for women defined as "high-risk" to be notified of increased risk after first-trimester screening, with the option of invasive prenatal testing; women in a "moderate-risk" category may receive second-trimester analyte screening to give an aneuploidy and ONTD risk assessment with the highest detection rate. Women identified as "low-risk" after first-trimester methods are not offered second-trimester analyte measurement in contingency screening [8].

The wide array of options may appear complicated to health care providers and patients alike; the benefits, limitations and possible scenarios for use are summarized in Table 8.4.

Other Outcomes

It is important to note that, while first-trimester screening provides a risk assessment for Down syndrome and trisomy 18, positive screens may lead to incidental diagnoses of other conditions. In one 10-year study, of 97 screen-positive pregnancies with abnormal fetal karyotypes, ~30 % had chromosome abnormalities other than trisomy 13, 18 or 21. Such findings included trisomy 16, triploidy, sex chromosome aneuploidies (45,X or Turner syndrome and 47,XYY), unbalanced translocations, and marker chromosomes. These clinical outcomes are expected to range from likely benign to lethal, underlining the importance of pretest and posttest counseling for the possibility of a chromosome anomaly other than the most common trisomies [46].

Table 8.4 Summary of first- and second-trimester maternal serum screening options [4, 5, 8]

Screening Method	Detection rate (DR)		Procedure	Advantages	Limitations	Clinician likely to utilize test
	Trisomy 21[a] (%)	Trisomy 18[b] (%)				
First-trimester analyte screening	62–63	~82	Free beta-hCG and PAPP-A drawn at 9–13 6/7 weeks	First-trimester result, NT not required, one visit, CVS an option if screen positive	Lower DR compared to options utilizing NT; no screening for ONTD	Clinician with early-to-care population with no access to certified NT provider, but does have access to CVS, and prefers one visit for screening
Combined first-trimester screening	78–91	91–96	Nuchal translucency ± nasal bone measurement and trimester analyte screening at ~10–13 6/7 weeks	First-trimester result, one visit, CVS an option if screen positive	NT required, lower DR compared to integrated screen; no screening for ONTD	Clinician with early-to-care population who has access to certified NT provider and CVS, and prefers one visit for screening
Integrated screening	94–96	91–96	PAPP-A and NT measurement at ~10–14 weeks; AFP, hCG, uE3 and DIA drawn at 15–21 6/7 weeks	Highest DR of all maternal serum screening tests	Two visits and NT required; results given in second trimester	Clinician with early-to-care patient population who has access to a certified NT provider, but does not have access to CVS
Serum integrated screening	87–88	~82	PAPP-A only at ~10–14 weeks; AFP, hCG, uE3 and DIA drawn at 15–21 6/7 weeks	Highest DR for screening when NT is not available; NT not required	Two visits, results given in second trimester, lower DR compared to screens that include NT	Clinician with early-to-care population who does not have access to certified NT provider or CVS
Stepwise sequential screening	91–95	91–96	PAPP-A, b-hCG, and NT in first trimester; risk reported if elevated. If low risk, AFP, hCG, uE3, and DIA in second trimester	First-trimester result for highest risk patients allows option of CVS; DR higher than combined FTS while allowing for some first-trimester results	Two visits for most patients; NT required; lower DR compared to integrated screen	Clinician with early-to-care population and high follow-up compliance, with access to a certified NT provider and CVS, who wants information early enough to offer CVS if risk is high, and wants to avoid moderate risk group created by contingency screening

(continued)

Table 8.4 (continued)

Screening Method	Detection rate (DR)		Procedure	Advantages	Limitations	Clinician likely to utilize test
	Trisomy 21[a] (%)	Trisomy 18[b] (%)				
Contingency screening	91–92	91–96	PAPP-A, b-hCG, and NT in first trimester; results reported; high risk offered diagnostic testing, low-risk screening complete; moderate risk group receives AFP, hCG, uE3, and DIA in second trimester	First-trimester results for high- and low-risk patients, minimizing number of patients needing a second visit	Two visits for moderate risk group; NT required; Initial moderate risk group may not feel as reassured with second trimester negative screen result as initial low-risk group; no screening for ONTD in low-risk group	Clinician with an early-to-care population and high follow-up compliance who has access to a certified NT provider and to CVS, and who feels the benefit of a one visit screen for most patients outweighs the anxiety caused for patients who fall into the moderate-risk group and are later re-stratified to a low-risk group
Multiple marker serum screening	75–83	60–70	AFP, hCG, uE3, DIA (±ITA) drawn between 15 and 21 6/7 weeks	Allows for screening in women presenting for care after first trimester; one visit	Results given in second trimester; lower DR compared to screens involving first-trimester elements; risk of conflicting assessments if performed without knowledge of prior combined first-trimester screening[c]	Clinician with patients who present primarily in the second trimester for screening or patients whose insurance does not cover NT screening.
Noninvasive DNA screening (NIDS)[d]	>99	>97	Maternal blood sample drawn between 10 and 21 6/7 weeks[e]	First- or second-trimester result in one visit, NT not required, highest DR	New technology with shorter publication history and less information on payer coverage	Clinician comfortable with new technology who wants a screening test with high DR and low FPR that can be applied in first and second trimesters

[a]Typically at a 5 % false-positive rate (FPR) with a 1/270 cut-off for screen positive

[b]Typically at a 0.5 % FPR with a 1/100 cut-off for screen positive

[c] Per ACOG's screening guidelines, second-trimester multiple marker serum screening should not be performed following first-trimester analyte or combined screening; MS-AFP only for ONTD risk assessment is recommended [4]

[d]Some practitioners endorse combining measures from NIDS and first-trimester biochemical markers using Bayes' theorem to provide more accurate patient-specific risks and improved NIDS performance (particularly when fetal fraction is <4 %); however, the information necessary for this calculation (depth of sequencing, *Z*-score, and fetal fraction) are often not readily available from the suppliers of NIDS [66]

[e]In theory, maternal blood can be drawn any time after 10 weeks gestation; gestational ages at which NIDS has been validated may vary by laboratory

Noninvasive DNA Screening for Aneuploidy

The method of testing that utilizes cell free fetal DNA from the plasma of a pregnant woman to screen for aneuploidy in the fetus was previously known as noninvasive prenatal diagnosis (NIPD) or noninvasive prenatal testing (NIPT). Over time this terminology fell out of favor given that a result is not considered diagnostic. The term noninvasive prenatal *screening* (NIPS) then became the preferred designation [67]. We suggest the term noninvasive *DNA* screening (NIDS) as an alternative. Indeed, "prenatal screening" applies to any type of noninvasive technology including ultrasound and maternal serum screening. Hence we will utilize the term NIDS as this better distinguishes this technology from more traditional screening modalities.

Circulating cell free fetal DNA (ccffDNA) comprises approximately 3 % to 13 % of the total cell free maternal DNA [13]. The percentage of the total cell free maternal DNA that is fetal in origin is termed the *fetal fraction*. It is important to note that this "fetal DNA" is thought to be derived primarily from placental trophoblasts [68], and it is well known that chromosomal abnormalities may exist in the placenta that are not present in the fetus [69]. The ccffDNA is cleared from the maternal blood within hours after childbirth [70]. The fetal fraction varies among women and several factors including gestational age, multiple gestations, and BMI are known to affect the magnitude of this fraction [71–73]. The quantity of ccffDNA increases during the first trimester and is felt to be at a sufficient quantity to perform NIDS by approximately 9 weeks gestation [74]. Therefore most clinically available tests are available starting at 10 weeks gestation. While evidence suggests that high maternal BMI is associated with a lower fetal fraction, no clear BMI cut-off has been set to guide practitioners as to when a patient's BMI may result in an inability to perform this testing [73]. Because gestational age and multiple gestations affect fetal fraction and subsequently, interpretation of NIDS results, ACOG recommends performing a baseline ultrasound examination for any patient considering NIDS, prior to testing [75].

Several studies have attempted to delineate the accuracy of NIDS in samples of varying fetal fraction. These studies suggest that the methodology and bioinformatics utilized will affect the fetal fraction required to achieve high sensitivity and specificity [76]. The fetal aneuploidy status itself can also affect the fetal fraction; for example, trisomy 13 is associated with reduced fetal fraction due to a smaller placenta mass associated with this aneuploidy [77]. Brar et al. demonstrated that there was no significant difference in fetal fraction between those at low and high a priori risk for aneuploidy [78].

Test Methodologies

Two main methodologies for NIDS have been validated and introduced into clinical practice. The more common approach, known as massively parallel shotgun sequencing (MPSS), is accomplished through quantifying millions of cell free DNA fragments. Each cell free fragment is assigned to its chromosome of origin. The total quantity of cell free fragments from the patient's specimen is then compared to a reference genome. The result is positive if there is an overrepresentation of the chromosome in the patient's specimen compared to the reference. A large number of chromosome fragments must be counted in order to detect aneuploidy; this is especially important when the fetal fraction is low as the difference between aneuploidy and euploidy will be small. Sequencing biases depending on the guanine and cytosine (GC) base pair content of the DNA fragments necessitates adjustments to allow for DNA base composition [79, 80]. The MPSS approach could be used for detection of all aneuploidies, although clinical trials have only yet validated testing for nonmosaic chromosomes 21, 18, 13, and monosomy X. A related strategy known as targeted massively parallel sequencing (t-MPS) differs in that it selectively amplifies only the chromosomal regions of interest (i.e., 21, 13, 18) and then determines whether there is an excess of one chromosome relative to another [81].

Clinical laboratories that utilize massively parallel sequencing employ different interpretation strategies. A z-score may be calculated to determine the ratio of observed sequences from a given

chromosome of interest versus a reference chromosome; an elevated z-score is suggestive of trisomy for the chromosome of interest [18]. Some laboratories may determine a positive result using a single z-score threshold (i.e., z-score greater than or equal to 3) [18], while others utilize a dual threshold model in which risk is stratified into categories such as "aneuploidy suspected" (z-score between 2.5 and 4) and "positive" (z-score greater than 4) [16]. Results may be presented categorically or as a risk score (i.e.,1 in 10,000).

Another approach to NIDS is the targeted counting of specific DNA sequences. With this methodology only selected loci from the chromosomes of interest are sequenced. This methodology is also known as single nucleotide polymorphism (SNP) based NIDS. Several thousand SNPs are sequenced. Each specimen is then evaluated based on the hypothesis that the fetus is monosomic, disomic, or trisomic. The position of the SNPs on the chromosomes and the possibility that recombination may have occurred must be considered. Likelihood is then calculated that the fetus is either diploid ("normal"), aneuploid, or triploid. The advantage of this technology is distinguishing between maternal and fetal SNPs, which allows for the detection of triploidy and may identify regions of fetal chromosome homology that could indicate consanguinity or uniparental disomy [82]. However, there must be a sufficient quantity of informative SNPs to provide an accurate result. A risk score is generated for each chromosomal abnormality evaluated.

Test Performance

Initially NIDS included common autosomal aneuploidies, Down syndrome, trisomy 18, and trisomy 13. Several validation studies have been completed to assess test performance for these conditions. Although the achieved detection rates and false-positive rates vary slightly among the various studies, overall NIDS utilizing the MPSS approach (based on outcomes from eight studies) achieved detection rates of approximately 99 %, 97.6 %, and 89.2 % for Down syndrome, trisomy 18 and trisomy 13, respectively. Validation studies which utilized the t-MPS methodology (including outcomes from six studies) achieved detection rates of 99.4 %, 97.9 %, and 81.8 % for Down syndrome, trisomy 18, and trisomy 13, respectively. The SNP-based approach (based on outcomes of two studies) achieved detection rates of 100 %, 96.4 %, and 100 % for Down syndrome, trisomy 18, and trisomy 13, respectively. However, the total number of aneuploidy cases included in the SNP-based studies was smaller (124 total cases) compared to that of the studies using t-MPS (274 total cases) or MPSS (680 total cases) approach. All three methodologies achieved low false-positive rates for the common aneuploidies, ranging from 0 to 0.32 % [81]. The positive predictive value (PPV) of a high-risk NIDS result was evaluated as part of the Comparison of Aneuploidy Risk Evaluations (CARE) study, a prospective, blinded, multicenter observational study comparing results of NIDS (performed by MPSS) with those of conventional screening for trisomy 21 and 18 in a general obstetrical population . The PPV with NIDS was 45.5 % for trisomy 21 versus 4.2 % with standard screening. The PPV with NIDS was 40 % for trisomy 18 versus 8.3 % with standard screening [20]. In a Chinese cohort of women younger than 35 years old 1741 samples were analyzed with NIDS (performed by MPSS) and an overall PPV of 86.67 % was calculated for the aneuploidy samples of all five chromosomes evaluated (21, 18, 13, X, and Y). This was compared to a PPV of 2.41 % with standard serum screening [21].

Testing for non-mosaic 45,X was subsequently evaluated by several groups. However, sample sizes in these studies were small and may have included ascertainment bias through preferential inclusion of nonviable cases and those with abnormal serum and/or ultrasound findings [81]. Observed detection rates for 45,X ranged from 75 % [16] to 91.5 % [83] using MPS methodology. Using a SNP-based methodology a detection rate of 92 % was achieved [84].

More recently, testing for sex chromosome aneuploidies and select microdeletion syndromes have been added to the test panels available through some commercial laboratories. However, robust estimates of the efficacy of testing for these conditions are not yet available and given the rarity of these disorders, positive predictive

values are expected to be low [85]. When considering sex aneuploidies and microdeletions, it is also important to keep in mind that these conditions are more likely than the traditional aneuploidies to be present in the mother. For example, age-related loss of an X-chromosome can lead to somatic mosaicism for 45,X cells [86].

Initially clinical validation studies of NIDS primarily focused on women identified as being at high risk for aneuploidy either by maternal age, abnormal serum screening, or abnormal ultrasound findings. More recently, studies have attempted to determine whether the performance of NIDS would be similar in a general obstetrical population. In a cohort of over 2000 women undergoing routine first-trimester aneuploidy screening a detection rate of over 99 % and false-positive rate of <1 % was found for trisomies 21 and 18, a similar performance to that observed in high-risk cohorts [87]. Pergament et al. evaluated the performance of SNP-based NIDS in samples from 1052 women, 49 % of which were low risk for aneuploidy. The study found that sensitivity and specificity for trisomy 21, 18, 13, and monosomy X did not differ between low-risk and high-risk populations [88]. The question, therefore, has been raised whether this should be applied to the entire population [89].

Some laboratories that perform NIDS with MPS methodology offer testing for twin gestations. Testing for monozygotic twins is expected to perform similarly to a singleton gestation. Testing in dizygotic twin and higher-order multiple gestations is complicated by the fact that the per-fetus fetal fraction may be lower. In fact, the non-reportable rate is higher (7.4 %) than that for singleton pregnancies (2 %) [90]. Additionally, if one fetus is euploid while the other is aneuploid, there is a dilution of the ccffDNA from the aneuploidy fetus resulting in decreased detection rates compared to singleton gestations [91].

Failure to obtain a NIDS result occurs in a small proportion of patients and may occur for a variety of reasons. The most common cause for test failure is insufficient fetal fraction in the maternal plasma specimen. This occurs in 2 % or less of patients undergoing NIDS with MPS methodology [90] and approximately 8 % of patients undergoing the SNP-based method, although the no-call rate of SNP-based methodology may be reduced by inclusion of a paternal specimen [88]. A low fetal fraction obtained in the initial sample is associated with a relatively high chance of failure with a second sample. Wang et al. evaluated 135 cases of test failure due to insufficient fetal DNA which were re-drawn, and found that 44 % of these patients had insufficient fetal DNA in their second specimen [73]. A study by Pergament et al. that evaluated the performance of SNP-based NIDS in both high and low risk cohorts, found that a non-reportable sample was 2.5 times more likely to be aneuploid [88]. Therefore, it is appropriate to consider invasive diagnosis rather than re-draw of NIDS in women with low fetal fraction, especially in cases where there is high risk of aneuploidy and gestational age is advanced.

Test Interpretation

Negative (low-risk) NIDS results should be carefully interpreted in the context of the patient's other clinical information including age, MSS results, family history and fetal ultrasound findings. Patients 35 years of age or older (advanced maternal age) should be informed that NIDS covers only the most common fetal aneuploidies seen in the advanced maternal age population. A study by Grati et al. investigated the proportion of clinically relevant chromosome abnormalities which are part of traditional prenatal screening (i.e., trisomies 21, 18, 13, monosomy X, triploidy). As part of the study 1, 178 abnormal karyotypes were identified among patients undergoing CVS or amniocentesis due to advanced maternal age. Approximately 24 % (280/1178) of these abnormal karyotypes (including autosomal aneuploidies, unbalanced structural rearrangements, supernumerary marker chromosomes containing euchromatic material, fetal mosaicism, and apparently balanced de novo reciprocal translocations) were not covered by traditional prenatal screenings [92]. Patients who have an abnormal MSS result should be informed that although those results indicate a risk for a specific aneuploidy, other aneuploidies and fetal conditions that are not covered by NIDS can present with an abnormal MSS [46].

It is recommended that patients who have other factors suggestive of a fetal aneuploidy

have genetic counseling and be presented with the option of invasive prenatal diagnosis regardless of NIDS results. This is important because NIDS does not screen for all chromosomal or genetic conditions. Indications for invasive prenatal diagnosis regardless of NIDS results include the presence of ultrasound abnormalities and personal or family history of a chromosome abnormality. Patients with other risk factors such as AMA, abnormal MSS, and ultrasonographic soft markers may also benefit from detailed counseling regardless of their NIDS results.

Positive (high-risk) NIDS results should be followed up with confirmatory invasive prenatal diagnosis for definitive fetal karyotyping. While some patients may decline confirmatory testing due to the procedural risk for miscarriage, it is not recommended that patients make decisions regarding pregnancy termination without confirmatory testing. This is important because false-positive results can occur. Several false-positive results have been reported with biological basis, such as confined placental mosaicism (CPM), maternal chromosome abnormality, vanishing twin, maternal cancer [93], and chromosomal microduplication/microdeletion syndrome [94, 95]. Concern for CPM makes amniocentesis, rather than CVS, the preferred choice for invasive prenatal diagnosis to clarify a positive NIDS result. A flow-chart summarizing our recommendations in cases of positive NIDS is outlined in Fig. 8.1.

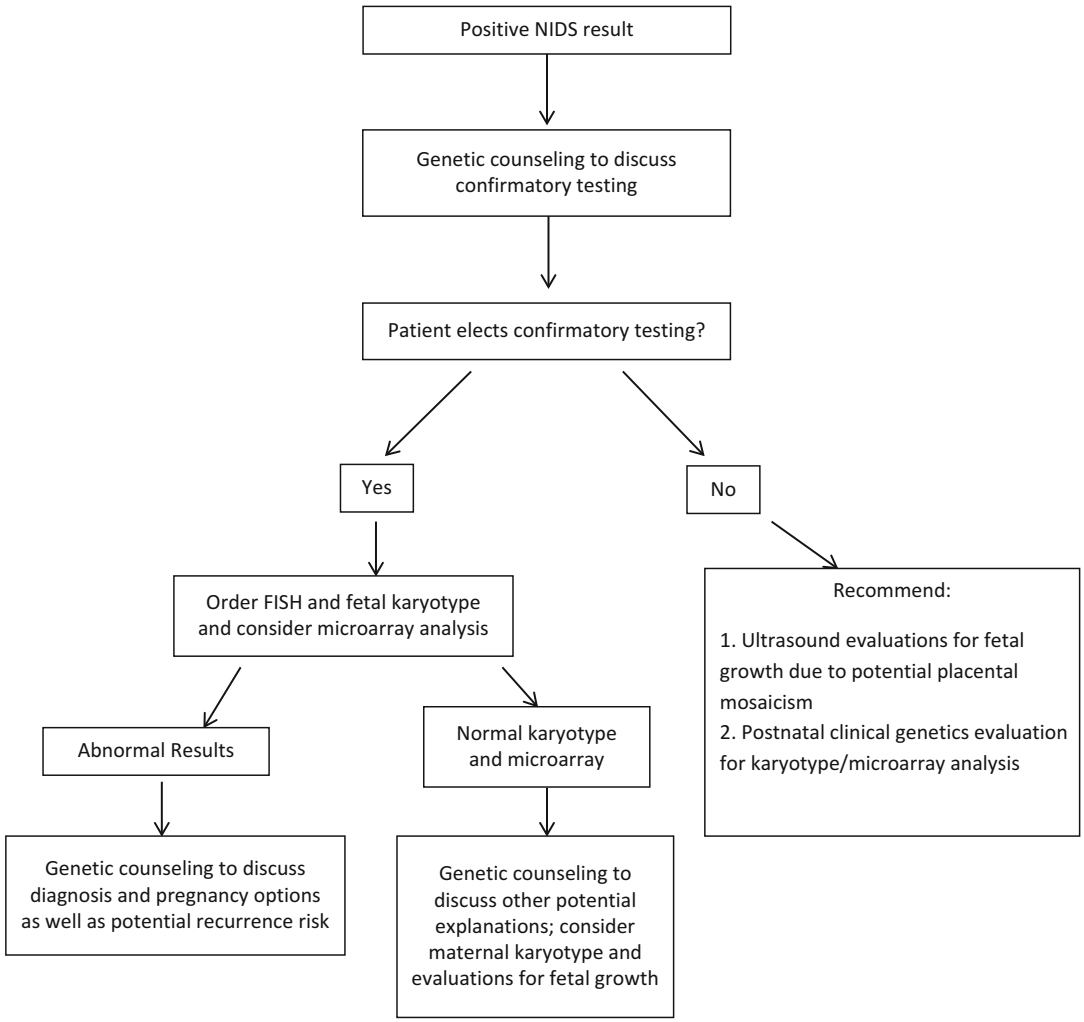

Fig. 8.1 Recommended follow-up of a positive NIDS result

Given the complexities of NIDS it is important that women receive adequate pre and post-test counseling with a qualified healthcare provider. The American College of Obstetrics and Gynecology, American College of Medical Genetics, International Society for Prenatal Diagnosis and National Society of Genetic Counselors have all released statements which outline the appropriate utilization of NIDS, including information which should be provided to the patient in order to obtain informed consent. A summary of these recommendations is included in Box 8.1.

Box 8.1 Key Points Required in Pretest and Posttest Counseling Regarding NIDS

- NIDS provides highly sensitive and specific screen results for the common autosomal aneuploidies (trisomy 21, 18 and 13) in singleton gestations after 9 weeks gestation. However, results are not considered diagnostic as false-positives and false-negative results do occur.
- The clinical validity of NIDS has been largely studied in a high-risk population (i.e., AMA, abnormal ultrasound or MSS), although limited evidence has suggested performance is similar in a low-risk population.
- Some clinically available NIDS includes evaluation for select chromosomal microdeletions; however, the sensitivity and specificities for these conditions is still being elucidated and depends on size of the deletion.
- A positive NIDS result requires genetic counseling and confirmation by invasive prenatal diagnosis (preferably amniocentesis) for fetal karyotyping.
- NIDS should not be considered a replacement of invasive prenatal diagnosis as results are not definitive and screening is performed only for a select number of aneuploidies. A family history should be reviewed to determine if the patient should be offered other forms of screening or prenatal diagnosis for a particular disorder.
- Although there are studies suggesting the efficacy of NIDS in multiple gestations, these studies included a small number of patients.
- In a proportion of cases there is insufficient fetal fraction or test failure for some other reason. There is some evidence to suggest that the risk of aneuploidy may be higher among women receiving a failed or un-interpretable result.
- In cases where mosaicism is present or there has been early demise of a co-twin, results may be inaccurate.

Other Considerations

The high sensitivity and specificity achieved by NIDS has the potential to reduce the number of procedure related losses of euploid fetuses. Garfield and colleagues used the results of the "MatErnal bLood IS Source to Accurately diagnose fetal aneuploidy (MELISSA)" Study Group to develop a model for evaluating the impact of NIDS if incorporated into routine prenatal care for all high-risk women. This model estimated that use of NIDS would result in a 66 % reduction in miscarriages related to invasive prenatal diagnosis and lead to 38 % more women receiving a prenatal diagnosis of Down syndrome. In addition the model estimated that total costs for prenatal screening and invasive diagnosis would be slightly decreased (by 1 %) annually [96].

Which Screening Test to Choose?

As with traditional maternal serum screening, there are distinct advantages and disadvantages to each of the NIDS testing methodologies. Although each laboratory includes an assessment for common aneuploidies (i.e., trisomies 21, 18,

and 13), there are differences among laboratories in the inclusion of sex aneuploidies and microdeletion/duplications. Some methods may not be optimal or available for certain patients or groups of patients; therefore, test selection should be made by a qualified provider. Table 8.4 summarizes advantages, disadvantages, and limitations of various screening modalities.

The Future of First-Trimester Aneuploidy Screening

Given the wealth of literature supporting the sensitivity and specificity of NIDS as well as the rapid incorporation of this screening tool into clinical practice, it is clear that NIDS is here to stay. The question has been raised about the role of first-trimester ultrasound with NT measurement and nasal bone evaluation in the setting of routine NIDS. First-trimester ultrasound remains a valuable and potentially cost-effective means of early detection of fetal structural anomalies (such as cardiac defects), accurate determination of gestational age, assessment of multiple gestations, comprehensive evaluation of the uterus and adnexa, and prediction of adverse maternal-fetal complications, in addition to being a screening tool for fetal aneuploidy and clarifying NIDS results [97].

While some NIDS platforms evaluate for a limited number of microdeletion/duplication syndromes, currently they do not report genome-wide findings of CNVs; this highlights the importance of first-trimester NT measurement in increasing suspicion for these conditions in the fetus. The clinical utility of traditional first-trimester screening modalities including ultrasound and serum biochemical screening is still compelling.

The future of aneuploidy screening will likely focus on how to incorporate these various components to achieve the highest sensitive/specific and cost-effective screening strategy. For example, based on a modeled analysis, Kagan and colleagues propose a contingent screening policy incorporating ductus venosus pulsatility index for veins (DV-PIV) along with nuchal translucency and maternal age. Those with an "intermediate" risk of aneuploidy (>1:3000) would undergo NIDS; those at "high risk" (>1:10) would undergo invasive prenatal diagnosis and fetal karyotyping. This model, based on data for population-based screening, improves cost effectiveness as compared to NIDS only, while maintaining a similar detection rate (96 % for Down syndrome, 95 % for trisomy 18, and 91 % for trisomy 13) [98]. This highlights the importance of first-trimester ultrasound as part of newer screening protocols incorporating NIDS. With the continued advancements in NIDS technology these strategies will need to be continually reevaluated and developed over time.

Patient Considerations and Perspectives

There is a paucity of literature addressing patients' attitudes towards prenatal screening, and the perceived "value" of these tests. While some studies attempt to estimate the value of screening in terms of "average cost per Down syndrome birth avoided" [97, 99], the psychosocial, ethical, and emotional aspects of screening are more difficult to quantify.

Some studies have examined the preferences of pregnant women with regard to the methods of screening. In one such study, 19.2 % of women opted out of screening; of those that opted in, 97.8 % preferred first rather than second-trimester screening [100]. A criticism of first-trimester screening is that some women with increased fetal NT will experience pregnancy loss, and therefore are exposed to "unnecessary" decisions about invasive testing and pregnancy termination. It should be noted, however, that in another study 69 % of women stated they would still choose NT screening regardless of risk of miscarriage, citing value in the knowledge of an underlying reason for a pregnancy loss, should one occur [101]. Early knowledge of fetal disorders has been shown to improve preparation of parents, and reduces physical and psychological trauma in cases of elective termination; therefore the provision of first-trimester screening is felt by some to

significantly enhance the autonomy of pregnant women [102–104].

Lenhard et al. found that mothers of children with Down syndrome, diagnosed prenatally, felt discriminated against, as if others implied that the birth of their child "should have been 'avoided'" via prenatal diagnosis and selective termination of pregnancy [105]. Accordingly, they found that mothers of children with Down syndrome tended to experience the availability of prenatal screening and diagnosis as an emotional burden. However, the improved medical care and psychosocial support for children with Down syndrome and their families may outweigh the emotional stress caused by the option of prenatal screening and diagnosis [106].

Skotko collected opinions regarding prenatal screening and diagnosis from 141 mothers who received a prenatal diagnosis of Down syndrome for their children via amniocentesis. He found that most respondents reported that their birthing experience was positive following a prenatal diagnosis of Down syndrome; by contrast, mothers who learned about the diagnosis after birth labeled their experience as negative [107]. This may be because mothers who receive a prenatal diagnosis may have the chance to resolve any grief prior to their child's birth. Mothers surveyed felt that results of maternal serum screening should be explained as a risk assessment, with Down syndrome being first explained after the results of a screening test, before invasive prenatal diagnosis is undertaken. Sensitive, accurate, and consistent messages about the range of ability in Down syndrome should be included.

As no therapeutic or curative intervention yet exists for Down syndrome or other chromosomal anomalies, prenatal screening exists to allow women to prepare for the birth and care of a child with chromosome anomalies, create a plan for special-needs adoption, or to pursue the option of pregnancy termination. Based on the results of the survey by Skotko, it is important for healthcare providers to note that not all women who consent to screening believe that having a child with a chromosome anomaly would be an undesired outcome, or would ultimately terminate a pregnancy for this reason. Mothers are more likely to want to consider all options and understand the known prognosis for children with Down syndrome, and gather as much information as possible before making a decision [108]. All reasons for prenatal screening and diagnosis, including reassurance, advance awareness before delivery of a child with a chromosome anomaly, adoption, and pregnancy termination should be discussed with patients in a nondirective manner. Up-to-date information and contact with local support groups for chromosome abnormalities such as Down syndrome should be provided [107].

Teaching Points

- Multiple methods of aneuploidy screening exist, with varying detection rates, benefits and limitations. These differences may help guide a practitioner to choose a method that is best suited to their patient population based on geography, costs, and socioeconomic factors.
- First-trimester ultrasound is beneficial, including NT assessment when available, even if maternal biochemical screening is not pursued, as it can provide dating information and risk assessment for nongenetic anomalies and pregnancy outcome.
- Ideally, informed consent via pretest counseling should be obtained prior to screening to ensure patients' understanding of the nondiagnostic, risk assessment nature of first-trimester screening and the possibility of identifying a high risk for conditions other than trisomies 13, 18 and 21.
- Based on the available literature, first-trimester screening is preferred over second-trimester screening by patients, and may serve to increase patient autonomy and improve outcomes for families delivering a child with a prenatally diagnosed chromosome anomaly.
- Noninvasive DNA screening (NIDS) via cell free fetal DNA analysis provides highly sensitive and specific screen results for the common autosomal aneuploidies (trisomy 21, 18, and 13) in singleton gestations after 9 weeks gestation. However, results are not considered

diagnostic as false-positives and false-negative results do occur.

- Because gestational age and multiple gestations affect fetal fraction and subsequently, interpretation of NIDS results, ACOG recommends performing a baseline ultrasound examination for any patient considering NIDS, prior to testing.
- The clinical validity of NIDS has been largely studied in a high-risk population (i.e., AMA, abnormal ultrasound or MSS) although limited evidence has suggested performance is similar in a low-risk population.
- A positive NIDS result requires genetic counseling and confirmation by invasive prenatal diagnosis (preferably amniocentesis) for fetal karyotyping.
- NIDS should not be considered a replacement of invasive prenatal diagnosis as results are not definitive and screening is performed only for a select number of aneuploidies. A family history should be reviewed to determine if the patient should be offered other forms of screening or prenatal diagnosis for a particular disorder.

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Fetal Biometry in Early Pregnancy

9

Lea M. Porche, Steven Warsof, and Alfred Abuhamad

Introduction

Fetal biometry, morphometric measurements of the fetus and gestational structures, has routinely been utilized in the second trimester for the determination of gestational age, estimation of abnormalities in fetal growth and weight, and determination of normal and abnormal fetal anatomy. With improvements in ultrasound technology, biometry in the first trimester has become a more accurate and useful tool. Many structures can be measured in the first trimester and are now able to give clues regarding pregnancy location, viability, gestational age, chorionicity in multiple gestations, and the risk of aneuploidy. In this chapter, we review the assessment of these structures and their significance in the first trimester.

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Biometry

Gestational Sac

As the earliest sonographic evidence of intrauterine pregnancy, the gestational sac (GS) can be seen as early as 4 weeks of gestation, just days after the first missed menses [1]. The GS can also be used in early pregnancy for assessment of dating [2]. When seen at 4 weeks, the gestational sac is about 2–3 mm in diameter and in this early phase grows rapidly at a rate of about 1 mm per day [3] (Table 9.1).

One measurement that has been used with high accuracy is the mean sac diameter (MSD). This measurement is obtained by taking the average of the measurements of the GS in three planes: coronal, sagittal, and transverse [1]. The MSD is useful early in the first trimester, but loses accuracy when it becomes greater than 14 mm, at which time the fetal pole should become visible. When measuring the dimensions of the GS, calipers should be placed on its borders and care should be taken to avoid including the surrounding decidual tissue [4] (Fig. 9.1).

Caution must be exercised in differentiating a true gestational sac from a pseudosac or a small intrauterine fluid or blood collection, both of which can be associated with ectopic or failed pregnancies [1] (Fig. 9.2). A true GS should typically be located eccentrically within the endometrial cavity due to it being embedded within the decidual layer [1]. There should also be evidence

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Table 9.1 Relation between mean sac diameter (MSD) and menstrual age[a]

Mean sac diameter (mm)	Predicted age range (weeks) = 95 % CI
2	5.0 (4.5–5.5)
3	5.1 (4.6–5.6)
4	5.2 (4.8–5.7)
5	5.4 (4.9–5.8)
6	5.5 (5.0–6.0)
7	5.6 (5.1–6.1)
9	5.9 (5.4–6.3)
10	6.0 (5.5–6.5)
11	6.1 (5.6–6.6)
12	6.2 (5.8–6.7)
13	6.4 (5.9–6.8)
14	6.5 (6.0–7.0)
15	6.6 (6.2–7.1)
16	6.7 (6.3–7.2)
17	6.9 (6.4–7.3)
18	7.0 (6.5–7.5)
19	7.1 (6.6–7.6)
20	7.3 (6.8–7.7)
21	7.4 (6.9–7.8)
22	7.5 (7.0–8.0)
23	7.6 (7.2–8.1)
24	7.8 (7.3–8.3)

[a]Adapted from Daya S, Wood S, Ward S, Lappalainen R, Caco C. Early pregnancy assessment with transvaginal ultrasound scanning. Can Med Assoc J 144:441, 1991

of the "double ring" sign, which refers to two echogenic rings surrounding the gestational sac. These rings represent the chorionic cavity with its associated villi and the surrounding developing decidua [5] (Fig. 9.3). If eccentric location of the GS with a double ring sign are not seen in a woman with a positive pregnancy test, a viable intrauterine pregnancy cannot be excluded, but these findings should raise suspicion for abnormal or extrauterine pregnancy, and close clinical follow-up is indicated [6].

Yolk Sac

The yolk sac (YS) first appears within the GS at 5 weeks of gestation, and is frequently the first identifiable structure within the GS [1, 7, 8]. Functioning as the first nutritional and metabolic support for the developing embryo prior to establishment of the placenta, it also offers ultrasonographic confirmation of intrauterine pregnancy [9] (Fig. 9.4).

While usually apparent by week 5 of gestation, the YS may not be visible until later, when the MSD is closer to 8 mm [7]. It is connected to the embryo by the vitelline duct. When the

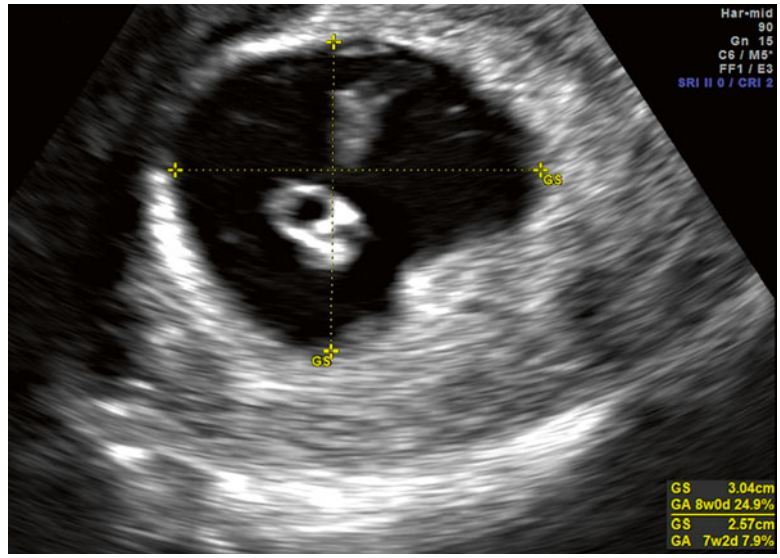

Fig. 9.1 The fetal pole and yolk sac can be seen within this gestational sac. Caliper measurements of the gestational sac are taken in the coronal and transverse planes. A third measurement will be taken in the sagittal plane to complete the three required measurements. The fetal crown-rump length will be used for the most accurate dating

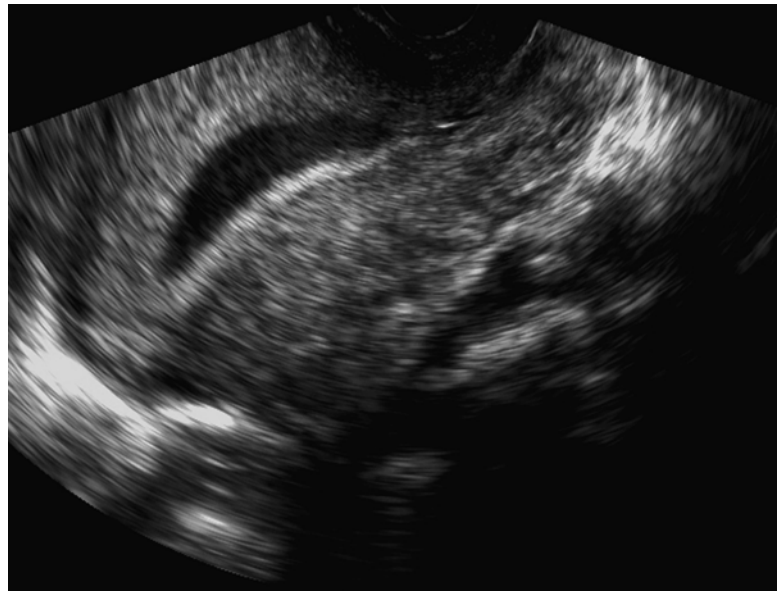

Fig. 9.2 This fluid collection within the uterus is a "pseudo sac" in the setting of an abdominal pregnancy. Note the central location and absence of two echogenic rings. These characteristics help to distinguish this from a true gestational sac associated with viable intrauterine pregnancy

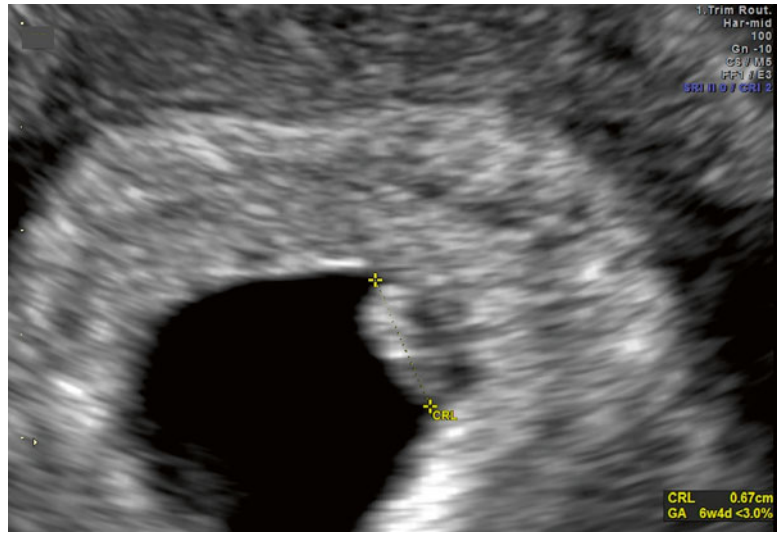

Fig. 9.3 "Double ring sign." The gestational sac can be seen with the eccentrically located fetal pole measured within. The two echogenic rings surrounding the gestational sac are clear in this image

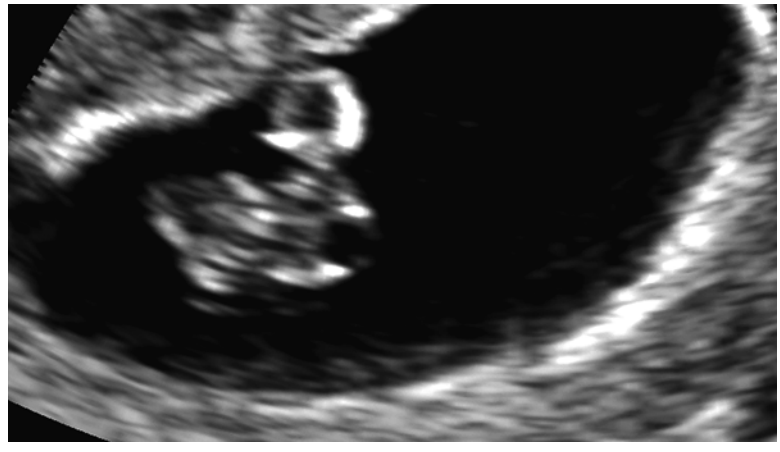

Fig. 9.4 Normal yolk sac. The yolk sac (above) can be seen in close proximity to the fetal pole (below). The hypoechoic developing rhombencephalon can be seen at the right end of the fetal pole

amnion forms around the fetus, the YS is then seen as an extra-amniotic structure. The YS progresses in size to a usual maximum of 6 mm around 10 weeks, and then regresses until it is absorbed between the amnion and chorion by the completion of week 12–13 [10]. Measurement of the YS should be performed by placing the calipers on the innermost border of the echogenic rim [11].

Nomograms relating YS size with gestational age have been developed [12], but due to marked variation in normal pregnancies, YS diameter should not be used a primary means of pregnancy dating [10].

As mentioned previously, the YS offers confirmation of intrauterine pregnancy, and can even help to indicate amnionicity in multiple gestations, as the number of YSs should correlate with the number of amniotic sacs if the embryos are viable [8]. This can be particularly important in higher order multiple gestations.

Marked variation in the size and shape of the YS can be noted. These variations may be of significance. A small or large YS (<3 mm prior to 6–10 weeks and >7 mm prior to 9 weeks) may be suspicious for an abnormally developing pregnancy. These cases should be followed up with repeat ultrasound evaluation to confirm progression of the pregnancy [1]. Absence of the YS or embryo in the presence of a MSD of ≥25 mm is diagnostic of a failed pregnancy with specificity and positive predictive value approaching 100 % [12]. Echogenic, irregularly shaped, or persistent YS, particularly after 12 weeks gestation, are of uncertain significance [13].

Crown-Rump Length

The fetal pole is first visible by transvaginal ultrasound at 5 weeks gestation with cardiac activity notable by 6–6.5 weeks gestation [1]. It is important to note that fetal heart rates can be slower than anticipated in these very early pregnancies, but should be within the normal range by 8 weeks gestation.

The first true fetal biometric measurement possible is the crown-rump length (CRL). By definition, the CRL is not actually measured from the fetal crown to its rump, but instead the longest linear dimension from the cephalic to the caudal end of the embryo with the fetus in neutral position (Fig. 9.5). In early gestation, between 6 and 9 weeks, fetal posture makes little difference in the CRL measurement, but beyond this point, flexion or extension can cause significant discrepancy.

Obtaining the CRL should be done in a standardized fashion to increase the accuracy of the measurement. A midsagittal section of the embryo

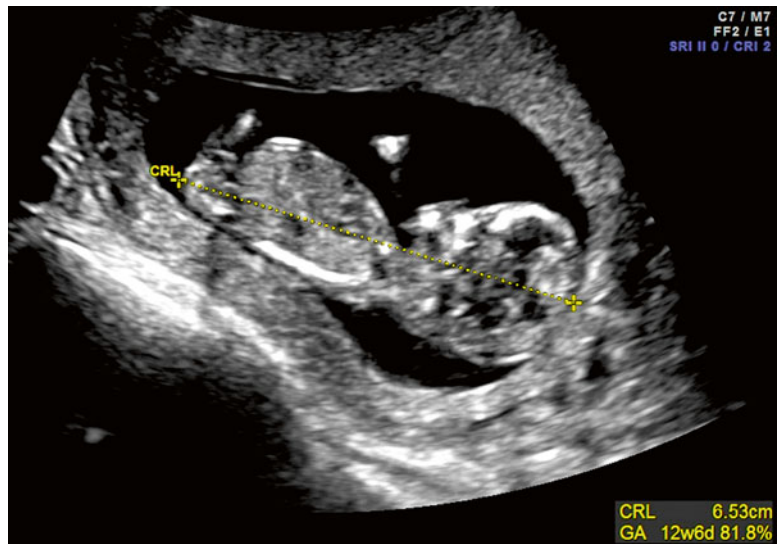

Fig. 9.5 Crown-rump length. Here the calipers are placed at the cephalic and caudal ends of the fetus. This fetus appears to be slightly flexed at the time of measurement

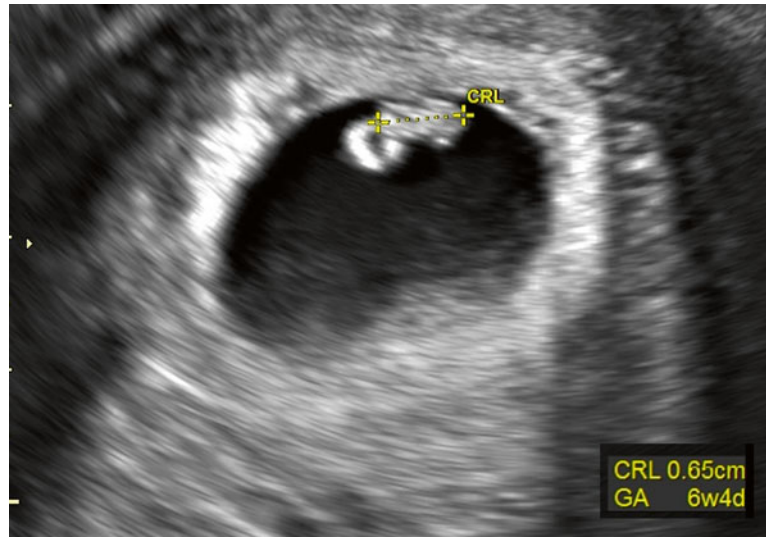

Fig. 9.6 Crown-rump length. This early crown-rump length measurement demonstrates the difficulty in identifying cephalic and caudal ends of the embryo at this early gestational age. Here, the greatest longitudinal measurement is obtained. The yolk sac can be seen in close proximity to the fetal pole

should be captured and the image maximized to fill the majority of the screen. Care should be taken to attempt capturing this image with the embryo in neutral position, avoiding hyperflexion or extension. The two ends of the embryo should be well defined, and the caliper function on the ultrasound machine used to capture the measurement. In extremely early gestations, the cephalic and caudal ends of the fetus may not be distinguishable. In this scenario, the greatest longitudinal measurement should be obtained [14] (Fig. 9.6).

The primary importance of the CRL measurement is in pregnancy dating. One of the first to pursue the biometric measurement of the fetal pole was Dr. Hugh Robinson, who worked with Professor Ian Donald at The Queen Mother's Hospital in Glasgow, Scotland. In early 1970s, he published works that gave validity to the use of ultrasound in the measurement of the early fetal pole. In one study, he evaluated women between 6 and 14 weeks gestation with regular cycles and known last menstrual periods by B-mode transabdominal ultrasound techniques [15]. He plotted his measurements against menstrual age, and in those with missed abortion, against the physical measurement of the conceptus after delivery. He noted a high degree of correlation between ultrasound measurements and menstrual age. Despite the most rudimentary of ultrasound equipment, his meticulous measurements have stood the test of time and are still used over 40 years later. Hence, first-trimester ultrasound with measurement of CRL is now considered the most reliable method of pregnancy dating with known and unknown last menstrual period. More recently, the accuracy of transvaginal ultrasound as a means for pregnancy dating was confirmed in a study by Pexters et al. showing that in 54 patients, CRL and MSD measurements showed high interobserver and intraobserver correlation, and were highly reproducible [16].

Many studies have been completed in different populations to assess the ability to generalize these initial nomograms. One such study was performed by Papageorghiou et al. in eight geographically different countries. Data from 4265 women were included to determine an equation that would be generalizable to multiple populations [17]. Many nomograms for CRL have been developed over the years. Based on the population, prediction equations can differ significantly. For example, the CRL curves developed by Robinson and Pexsters differ at very early gestations, but are very similar after about 8 weeks. Most published CRL curves differ very little from the measurement published by Dr. Robinson in 1973 (Tables 9.2 and 9.3).

Measurement of CRL can routinely be completed via transvaginal ultrasound by 6 weeks of gestation. When measured between weeks 7 and 10, CRL is proven to be accurate within 3 days of

Table 9.2 Gestational age estimation by crown-rump length (CRL): Robinson[a]

Fetal CRL (mm)	Gestational age (weeks + days)
5	6 + 0
10	7 + 1
15	7 + 6
20	8 + 4
25	9 + 2
30	9 + 6
35	10 + 2
40	10 + 6
45	11 + 2
50	11 + 5
55	12 + 1
60	12 + 3
65	12 + 6
70	13 + 1
75	13 + 4
80	13 + 6
85	14 + 1
Formula	GA (days) = 8.052 × (CRL × 1.037)1/2 + 23.73

[a]Adapted from Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol 1975; 82:702–10

Table 9.3 Gestational age estimation by crown-rump length (CRL): Pexsters[a]

Mean CRL (mm)	Gestational age (weeks + days)
0.4	5 + 5
1.1	5 + 6
1.9	6 + 0
2.7	6 + 1
3.5	6 + 2
4.3	6 + 3
5.2	6 + 4
6.1	6 + 5
7.0	6 + 6
8.0	7 + 0
8.9	7 + 1
9.9	7 + 2
10.9	7 + 3
12.0	7 + 4
13.1	7 + 5
14.2	7 + 6
15.3	8 + 0
16.4	8 + 1
17.6	8 + 2
18.8	8 + 3
20.0	8 + 4
21.2	8 + 5
22.5	8 + 6
23.8	9 + 0
25.1	9 + 1
26.4	9 + 2
27.8	9 + 3
29.2	9 + 4
30.6	9 + 5
32.0	9 + 6
33.5	10 + 0
35.0	10 + 1
36.5	10 + 2
38.1	10 + 3
39.6	10 + 4
41.2	10 + 5
42.8	10 + 6
44.5	11 + 0
46.1	11 + 1
47.8	11 + 2
49.5	11 + 3
51.3	11 + 4
53.0	11 + 5
54.8	11 + 6
56.6	12 + 0
58.5	12 + 1
60.3	12 + 2
62.2	12 + 3
64.1	12 + 4
66.1	12 + 5
68.0	12 + 6
70.0	13 + 0
72.0	13 + 1
74.0	13 + 2
76.1	13 + 3
78.2	13 + 4
80.3	13 + 5
82.4	13 + 6
84.6	14 + 0

[a]Adapted from Pexsters A, Daemen A, Bottomley C, Van Schoubroeck D, De Catte L, De Moor B, et al. New crown-rump length curve based on over 3500 pregnancies. Ultrasound Obstet Gynecol 2010; 35: 650–655

Table 9.4 Guidelines for redating pregnancy based on ultrasound in first trimester[a]

Gestational age range (weeks + days)	Method of measurement	Discrepancy between ultrasound dating and LMP dating that supports redating
≤13 + 6	CRL	
• ≤8 + 6		More than 5 days
• 9 + 0–13 + 6		More than 7 days
14 + 0–15 + 6	BPD, HC, AC, FL	More than 7 days
16 + 0–21 + 6	BPD, HC, AC, FL	More than 10 days

[a]Adapted from ACOG Committee Opinion 611: Method for Estimating Due Date, October 2014

actual gestational age [15, 18]. However between 10 and 14 weeks, the accuracy decreases slightly to a margin of ±5 days [19], and with the addition of just one more week, the accuracy at 15 weeks gestation is as wide as ±8 days [20]. This reinforces the fact that for the most accurate pregnancy dating, CRL should be measured between 7 and 10 weeks of gestation. Of note, once the CRL measures beyond 84 mm (about 14 weeks gestation) the biparietal diameter (BPD) has been proven to be more accurate in pregnancy dating [15]. While many complex formulas have been determined, an easy formula to correlate gestational age with CRL from 7 to 14 weeks gestation is:

$$\mathrm{GA}\left(\mathrm{weeks}\right) = 6.5 + \mathrm{CRL}\left(\mathrm{cm}\right)$$

When assigning a due date for early pregnancy, the American College of Obstetricians and Gynecologists (ACOG) have published criteria regarding what degree of discrepancy warrants a change in assigned due date. In the first trimester prior to 9 weeks gestation, the due date should be reassigned if the discrepancy between the ultrasound and menstrual dating is ±5 days. Between 9 and 15 + 6 weeks, dating should be reassigned based on a discrepancy of ±7 days [21, 22] (Table 9.4).

Nuchal Translucency

The importance of the nuchal translucency (NT) measurement in fetal medicine was first recognized by the pioneering work of Professor Kypros Nicolaides in the mid 1990s at King's College Hospital in London, UK. Measurement of the nuchal translucency is now recommended as an option for patients as a part of first trimester screening for aneuploidy [23]. One element of the first trimester screening exam, the NT measurement is combined with levels of maternal serum beta human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) [24]. These parameters together with maternal age give a patient-specific risk for trisomy 21 and 18. For trisomy 21, the detection rate is 85 % with a 5 % false-positive rate, which is higher than the detection rate in the second trimester using multiple maternal serum markers alone [25].

The NT is a hypoechoic structure located under the skin on the posterior fetal neck that represents fluid collection in that space [1] (Fig. 9.7). This structure can be identified and measured in all normal pregnancies, but the measurement is increased in cases of fetal aneuploidy or congenital heart disease. In monochorionic twins intertwin discrepancies in the NT measurement have been associated with early evidence of twin–twin transfusions syndrome [26].

There are multiple theories regarding the etiology of increased NT measurements. In trisomy 21, dermal collagen has more hydrophilic properties, trapping fluid in the subcutaneous tissues [3]. In Turner syndrome, dysplastic lymphatics are credited with obstruction of the normal flow of fluid out of this space. Abnormal lymphatic drainage can also arise in the absence of Turner syndrome, leading to increased NT, enlarged jugular venous sacs and subsequent increase in venous pressure that can be detected as decreased

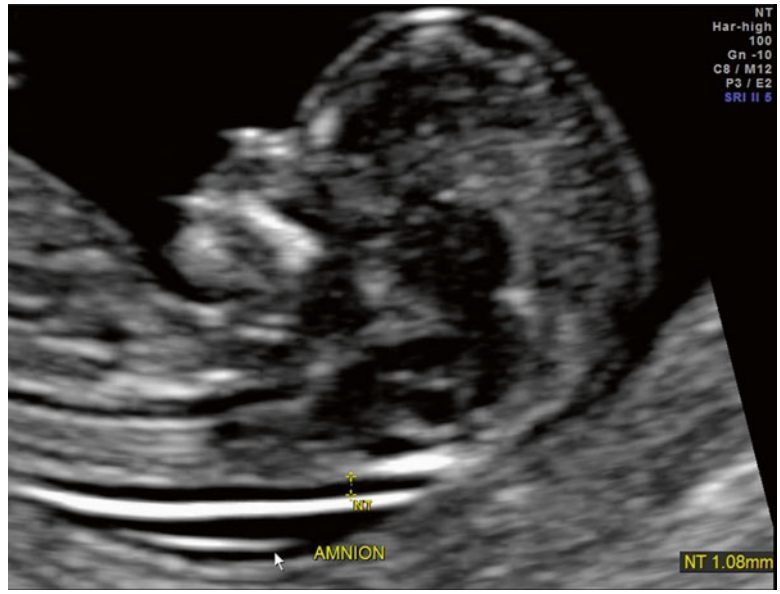

Fig. 9.7 Normal NT measurement. Here a normal NT measurement can be seen with all criteria met. Note the amnion that is clearly seen as separate from the posterior margin of the nuchal fluid collection

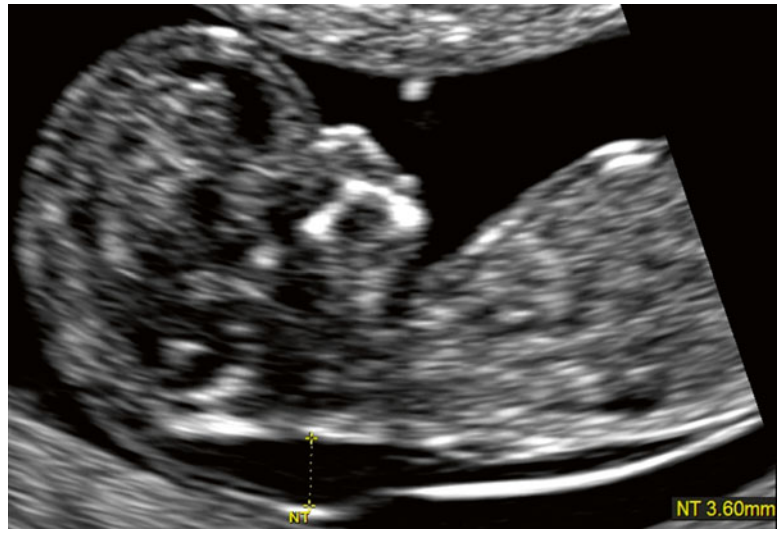

Fig. 9.8 Enlarged NT measurement. The enlarged NT can be well seen in this image. Note that the measurement is taken at the largest portion of the fluid collection

or absent end diastolic flow in the ductus venosus [27, 28]. Finally, it has been seen that an enlarged NT can be associated with congenital cardiac disease, especially septal defects. It is postulated that endothelial dysfunction is responsible for the concurrent appearance of these two abnormalities. Importantly, it has not been proven that an enlarged NT measurement is a sign of cardiac failure and it should not be considered a marker for hydrops [29] (Fig. 9.8).

Similarly, a cystic hygroma arises from obstruction of lymphatic flow into the venous system, leading to distention of the jugular venous sacs. Depending on the size of the cystic hygroma, it may be difficult to differentiate from an enlarged NT. While an enlarged NT is usually confined to the cervical region, cystic hygromas are usually larger and extend beyond the neck. They also often contain septations that make their appearance differ from that of an enlarged

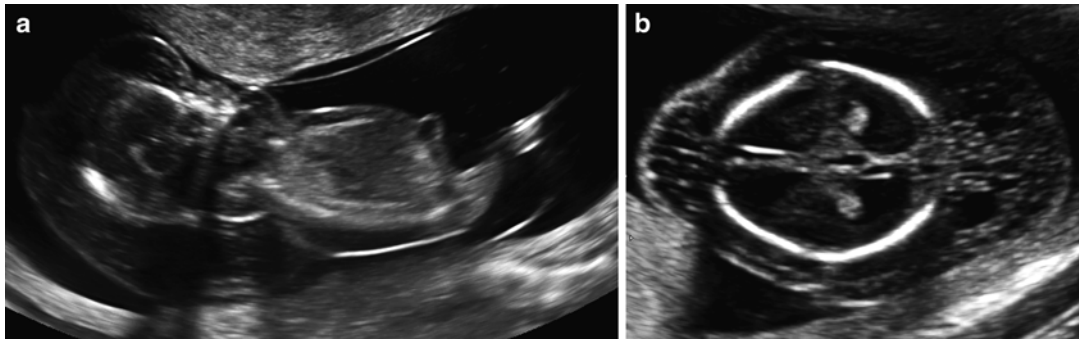

Fig. 9.9 (**a**) Cystic hygroma: sagittal view of a fetus with a cystic hygroma. This fluid collection is not confined to the posterior cervical region, but instead extends cephalad to the face and caudad to the sacrum and legs. In this image, the fetal head is on the *left*, and the legs and pelvis are to the *right*. (**b**) Cystic hygroma: an axial view of the same cystic hygroma. The bones of the calvarium can be seen with surrounding increase in soft tissue and fluid. Posteriorly (*right*), fluid pockets and septations can be seen

NT [30] (Fig. 9.9a, b). Care should be taken not to confuse posterior neural tube defects with a cystic hygroma, as they can be similar in appearance [27].

The differential diagnosis for conditions associated with an enlarged NT can be seen in Table 9.5. Enlargement of the NT measurement is defined in most settings as an NT measurement above the 95th percentile for gestational age or ≥3 mm [23].

Accurate acquisition of the NT measurement is of great importance. In fact, no other ultrasound measurement requires the precision needed for accurate assessment of aneuploidy risk. The measurement should be obtained between 11 and 13+6 week gestation which is equivalent to a CRL of 45–84 mm [14]. Images can be obtained transvaginally or transabdominally using a high-resolution ultrasound machine. A magnified midsagittal section through the head and upper torso must be obtained and captured with the fetus in neutral position. The echogenic tip of the fetal nose is an indicator that one is imaging through this midsagittal plane. The amnion, which has not yet fused with the chorion at this gestation, should be visualized to ensure that the measurement is only of the NT and does not include intramniotic fluid. The calipers should be placed on the inner margins of the thickest portion of the NT and this is where the measurement should be obtained. If multiple adequate images are obtained, the largest measurement should be used for determination of risk [14]. The criteria needed to obtain an accurate NT measurement are shown in Table 9.6. With such extensive criteria, it is

Table 9.5 Differential diagnosis for enlarged nuchal translucency (NT)[a]

Aneupoidy
• Trisomy 21
• Trisomy 13
• Trisomy 18
• Monosomy X
• Triploidy
Structural anomalies
• Cardiac defects
• Diaphragmatic hernia
• Renal anomalies
• Body stalk disruption
• Abdominal wall defects
Genetic syndromes[b]
• Noonan syndrome
• Roberts syndrome
• Cornelia de Lange syndrome
• Congenital adrenal hyperplasia
• Spinal muscular atrophy
• DiGeorge syndrome
• Smith–Lemli–Opitz syndrome
• Various skeletal dysplasias
Increased risk of twin-to-twin transfusion syndrome

[a]Adapted from Simpson LL. First trimester cystic hygroma and increased nuchal translucency, UpToDate 2014
[b]Not a comprehensive list

Table 9.6 Guidelines for measurement of nuchal translucency (NT)[a]

• Margins of NT clear enough for proper caliper placement
• Fetus in midsagittal plane
• Image magnified to be filled with fetal head, neck and upper thorax
• Fetal neck in neutral position
• Amnion must be seen separate from the NT
• Calipers must be used for measurement
• Calipers must be placed on the inner border of the nuchal line space with none of the horizontal crossbar protruding into the space
• Calipers placed perpendicular to the long axis of the fetus
• Measurement obtained at the widest space of the NT

[a]Adapted from the AIUM Practice Guideline for the performance of Obstetric Ultrasound Examinations, 2013

possible that an NT measurement cannot always be obtained. Some limiting factors are fetal position and maternal body habitus. If the NT cannot be obtained and first trimester screening cannot be completed, the patient should be offered alternative risk assessment for aneuploidy commensurate with her clinical scenario.

It is also important that a practice seeking to perform NT measurements is adequately equipped to acquire accurate images and to manage any abnormalities diagnosed. High-resolution ultrasound equipment should be available for use. Special training, certification, and maintenance of certification for those obtaining and interpreting the image are also required. Finally, appropriate counseling and follow up strategies should be in place to address abnormal results [14].

Follow-up of high-risk first trimester screening is of utmost importance in patient care. Genetic counseling should be made available so that patients can explore all of their options for genetic testing. For those wanting more definitive assessment of their risk, they can undergo a second screening test by evaluation of maternal cell-free DNA that yields a sensitivity of 99 % with a false-positive rate of 1 %. Late in the first trimester, prior to fusion of the chorion and amnion, the most common diagnostic test that is offered is chorionic villus sampling for direct evaluation of karyotype. Comparative genetic hybridization (CGH) studies can also be done to identify subchromosomal abnormalities at the same time. Later in the early second trimester, amniocentesis can be performed to obtain fetal cells for karyotype once the amnion and chorion have fused. If aneuploidy is unable to be ruled out with diagnostic testing, close ultrasound surveillance should be undertaken with detailed anatomic survey and fetal echocardiography in the second trimester [3]. Details on aneuploidy screening are available in Chap. 8.

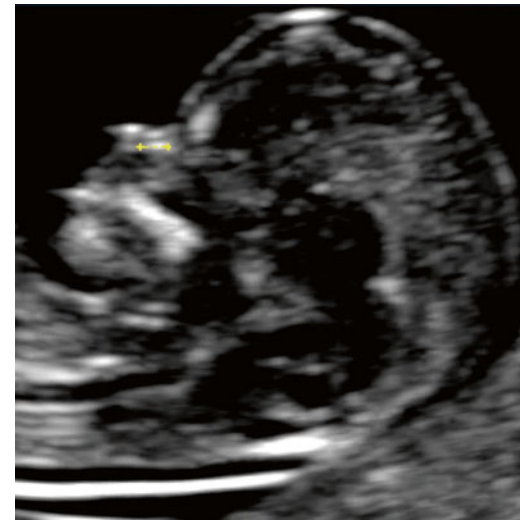

Fig. 9.10 Nasal bone. The hyperechoic nasal tip and skin can be seen with a normal nasal bone noted underneath. The angle of insonation is correct in this image. Note the additional landmark of the rectangular hard palate seen inferior to the nasal bone

Nasal Bone

The absence of the nasal bone (NB) is considered a soft marker for aneuploidy. A soft marker is a sonographic finding that can be associated with, but is not diagnostic of a fetal condition [31]. In the midsagittal plane, the NB is seen as a bright line of greater echogenicity than the skin (Fig. 9.10). The presence of the NB is best assessed at a CRL between 65 and 84 mm correlating to a gestational age of 13–13 + 5 weeks [32]. Criteria for measurement of the nasal bone can be seen in Table 9.7.

Table 9.7 Guidelines for measurement of nasal bone (NB)[a]

• Measured from 11 to 13+6 weeks gestation
• Fetal head, neck and thorax should occupy the entire image
• Measured in the midsagittal view
Echogenic tip of nose should be seen
Third and fourth ventricle seen
Rectangular palate should be seen
• Angle of insonation ~45° to fetal profile
• Brightness of NB equal to or greater than overlying skin

[a]Adapted from The Fetal Medicine Foundation, www.fetalmedicine.org

A hypoplastic or absent NB has been associated with trisomy 21. One publication reviewed over 35,000 NB examinations from nine different studies and showed that the NB was absent in 65 % of fetuses with trisomy 21 but only in 0.8 % of chromosomally normal fetuses [33]. In the second trimester, this marker becomes less predictive with absent NB seen in 30–40 % of fetuses with trisomy 21 and 0.3–0.7 % of chromosomally normal fetuses [34].

Different methods of reporting observations of the NB yield different results. Some report the NB categorically as "present" or "absent," while others measure it and report whether it is hypoplastic. Absent NB in the second trimester was seen in 30–40 % of fetuses with trisomy 21 and 0.3–0.7 % of chromosomally normal fetuses. By considering NB hypoplasia or absent nasal bone as a single category, the finding was seen in 50–60 % of fetuses with trisomy 21 and 6–7 % of chromosomally normal fetuses [34]. Other ways to report hypoplasia of the NB include an absolute cutoff of <2.5 mm, gestational age-related cutoff of <2.5th or <5th percentile, a ratio of BPD/NB length or multiples of the median for gestational age with <0.75 MoM being the cutoff for abnormal NB measurement [35, 36].

It is noteworthy that there is natural variation in the appearance of the NB. Absence of the NB at or before 13 weeks gestation can be a result of delayed ossification instead of absence or hypoplasia [37]. Similarly, ethnic variations exist in the presence and size of the nasal bone. In a study by Cicero et al. the likelihood ratio for trisomy 21 with an absent NB was higher in Caucasian women than in Afro-Caribbean women (likelihood ration of 31 vs. 9) [38]. These variations reinforce that assessment of the NB should not be used in isolation for diagnosis of trisomy 21. On the contrary, it has been used in combination with first-trimester serum screening and NT measurement to increase the detection of trisomy 21–90 % over the 85 % of first trimester combined screening alone [39].

Other Biometric Measurements

Four other biometric measurements are used in the second trimester to estimate gestational age or fetal weight. These measurements include the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). The combination of these four measurements for dating and estimation of fetal weight is usually begun starting at 14 weeks gestation, but there is some utility in measuring these parameters in the first trimester.

The measurement of BPD can be useful in the later portions of the first trimester when CRL measurements may be less accurate [18]. This decrease in the accuracy of the CRL may be due to normal changes in embryonic and fetal posture that can distort the CRL measurement. Head circumference can similarly be used in this scenario [40].

A BPD that is inconsistent with expected size may also be an indicator of fetal anomaly. Two studies have reported that small BPD values less than the 5th to 10th percentile may be associated with subsequent diagnosis of open spina bifida [41, 42].

By 10 weeks gestation, the femur can be identified and measured. Its measurement is usually accurate within 1 week of the fetus's true gestational age before 20 weeks gestation [40]. This makes it an ideal parameter for quick estimation of gestational age, but care must be taken in order to obtain an accurate measurement. One should be able to see the femoral head or greater trochanter proximally and the femoral condyle distally, and measurement should only include the ossified portion of the bone [43].

This measurement should not be taken in isolation, as it is known that there are some normal variations between ethnic groups. A FL less than the 5th percentile may also be a marker of aneuploidy (such as in trisomy 21) or an early indicator of fetal skeletal dysplasia or early growth restriction [44, 45].

Summary

Fetal biometry in the first trimester is important because it is our first evaluation regarding the health of a pregnancy. It can give clues regarding risk of fetal anomalies and aneuploidy. Understanding normal and abnormal measurements allows the clinician to accurately evaluate aberrations of early pregnancy and to counsel patients about physiologic and pathologic findings.

Teaching Points

- The gestational sac is the earliest ultrasound finding of an intrauterine pregnancy.
- First-trimester ultrasound evaluation is useful in identification of ectopic pregnancies.
- Failure of appropriate growth of GS and CRL are associated with early pregnancy failure.
- First-trimester measurement of the CRL is the most accurate ultrasound method of determining gestational age and EDC.
- Measurement of the nuchal translucency from 10 to 14 weeks gestation in combination with serum markers can be used for risk assessment for fetal aneuploidy.

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Threshold, Discriminatory Zone, and "The New Rules"

10

James M. Shwayder

Introduction

Early pregnancy evaluation markedly improved with the introduction of transvaginal sonography (TVS). Our understanding of early pregnancy growth has increased with improved resolution and imaging capabilities. As a result, a reevaluation of the threshold levels, discriminatory zone, and determination of early pregnancy failure has occurred, with dramatic changes in our recommendations.

Threshold Value

The threshold value is the lowest hCG level at which a normal intrauterine pregnancy (IUP) can be detected. Connolly et al. reevaluated the threshold value in a 2013 manuscript [1]. Previously, threshold values had been reported in the 500–1000 mIU/mL range. Connolly reported a 99 % probability of detecting a gestational sac at 390 mIU/mL (Fig. 10.1). Thus, the diagnosis of a normal IUP can be made earlier than previously assumed. However, this refined capability depends on the sophistication of the ultrasound equipment, the transducer frequency, uterine position, a patient's body habitus, and the operators experience and ability. Most modern equipment has vaginal probes with appropriate frequencies to detect very early pregnancies. However, a mid-plane uterus or one with numerous myomas may make visualization quite difficult. This author has found that body habitus also impacts the ability to adequately visualize the pelvic anatomy. If an ultrasound study does not resolve or clarify the clinical situation, referral to an expert sonographer with more sophisticated equipment is often of value. Finally, caution is warranted, as these guidelines are not applicable to patients with multiple gestations. This is particularly pertinent in patients who have undergone assisted reproduction.

Discriminatory Value

The discriminatory value is that level of hCG above which all normal intrauterine pregnancies should be seen. An early study, using transabdominal ultrasound, advocated a level of 6500 mIU/mL [2]. Clearly, the introduction of transvaginal sonography revolutionized early pregnancy assessment. In 1987, relatively early in the use of TVS, Nyberg et al. reported that the discriminatory level was 1800 mIU/mL (Third International Standard) [3]. As equipment improved the general consensus was that the discriminatory level was between 1000 and

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1500 mIU/mL in most centers. This level has become progressively more important with the increased adoption of medical management of ectopic pregnancy. Unfortunately, there are rising numbers of early IUPs being treated with methotrexate, being erroneously diagnosed as an ectopic pregnancy, based on the lack of an intrauterine gestational sac when the hCG is above the discriminatory value. This clearly has both medical and legal implications [4]. The reliance on the previous discriminatory values was contested in a paper by Doubilet and Benson in 2011 [5]. This retrospective review assessed the hCG level in 202 patients evaluated over 10 years, who had a TVS and β-hCG on the same day, had no visualized intrauterine fluid collection on their initial study, but were subsequently found to have an intrauterine pregnancy, with embryonic fetal cardiac activity. They found that 10.4 % of such pregnancies had an hCG > 1500 mIU/mL, with 4.5 % having an hCG above 2000 mIU/mL (Fig. 10.2). This challenged the medical community to reevaluate our current hCG discriminatory level. Connolly et al., in 2013, reported on 651

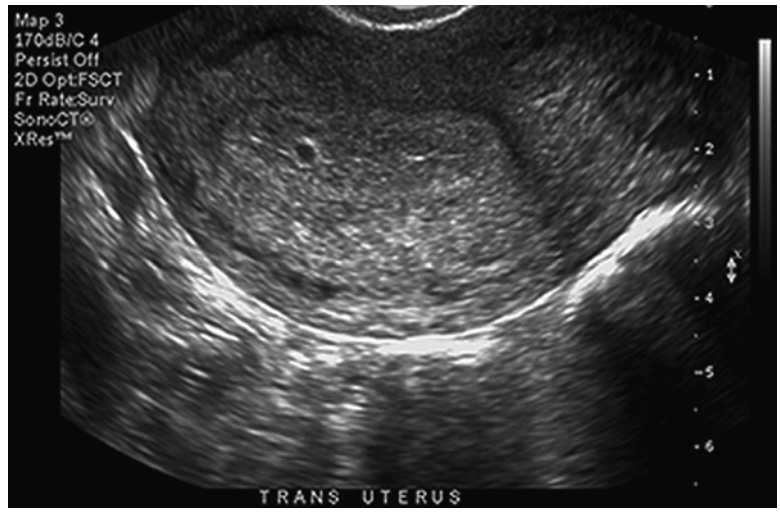

Fig. 10.1 Early gestational sac with hCG = 420 mIU/mL

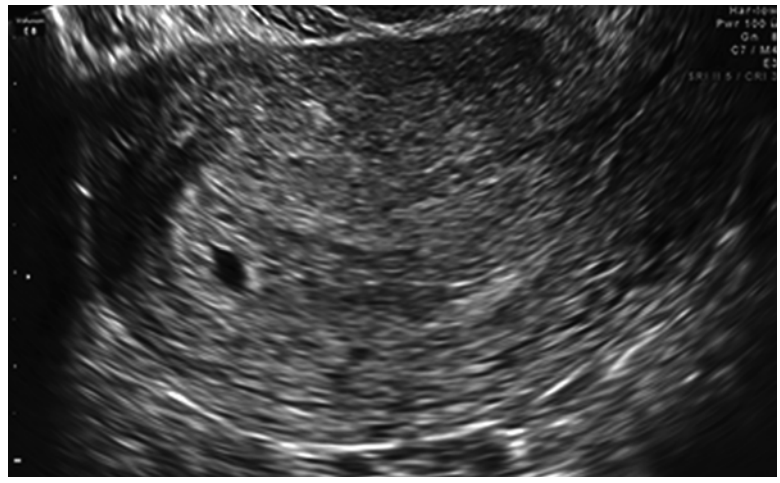

Fig. 10.2 Gestational sac finally visualized when the hCG = 1570 mIU/mL

patients with known intrauterine pregnancies who had a TVS and β-hCG within 6 h of each other. They evaluated the initial ultrasound findings which were visualized 99 % of the time, in correlation with the hCG level (Table 10.1). They determined that the discriminatory value was 3510 mIU/mL, much higher than previously advocated. It is estimated that women with an hCG above 2000 mIU/ML and no visualized gestational sac are more likely to have a nonviable intrauterine pregnancy (65 %) than an ectopic pregnancy (33 %), with the remainder (2 %) being viable intrauterine pregnancies. Thus, in a patient with a pregnancy of unknown location [6], with an hCG level over 2000 mIU/mL and who is hemodynamically stable, observation and follow-up are recommended until the clinical diagnosis is clarified (Fig. 10.3) [7, 8].

Table 10.1 Threshold and discriminatory values in 99 % of intrauterine pregnancies [1]

hCG (mIU/mL)	Gestational sac	Yolk sac	Embryo
Threshold value	390	1094	1394
Discriminatory value	3510	17,716	47,685

The "New Rules" Regarding Early Pregnancy Failure

Several developmental milestones are observed in normal intrauterine pregnancy, including an intrauterine sac at 5 weeks; a yolk sac at 5.5 weeks, and an embryonic pole and fetal heart activity at 6–6.5 weeks of gestation [9, 10]. Early pregnancy failure was felt to be present when these milestones were not met. However, there is significant interobserver and intraobserver variability (±18.78 %) in measuring the mean sac diameter, and the crown-rump length [11]. As a result, there are recognized limitations of our current definitions of a nonviable pregnancy based on ultrasound evaluation [12]. Abdallah et al. evaluated 1060 women with a diagnosis of an intrauterine pregnancy of unknown viability, of which 473 (44.6 %) remained viable and (55.4 %) nonviable by the 11- to 14-week scan. There was a 4.4 % false-positive rate for a nonviable pregnancy using the traditional cutoff for mean sac diameter (MSD) of 16 mm. This rate dropped to 0.5 % using 20 mm, with no false positives when a MSD of ≥21 mm was used. Considering the inherent variability identified, these authors recommended a cutoff for MSD ≥ 25 mm, a level where no false positives

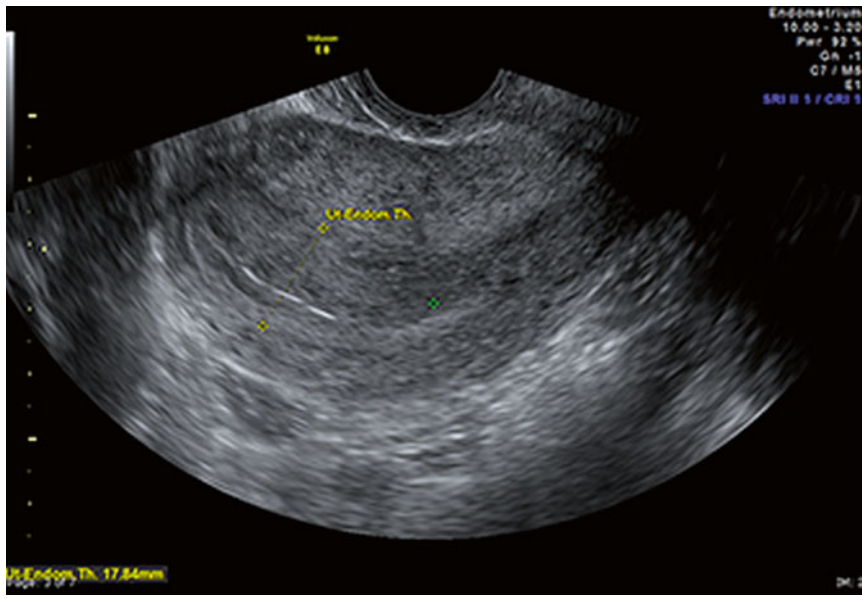

Fig. 10.3 Pregnancy of unknown location with hCG = 3810 mIU/mL. Patient ultimately had IUP with twin gestation

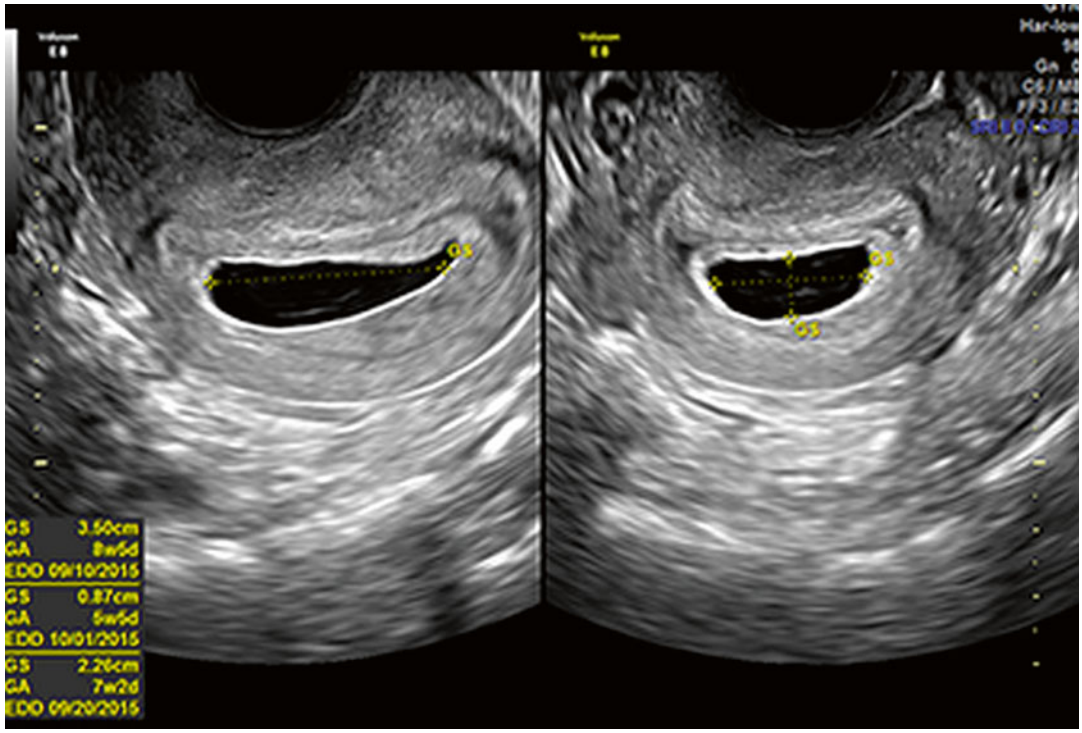

Fig. 10.4 Anembryonic pregnancy with gestational sac with a mean average diameter of 2.2 cm. No yolk sac or embryo was identified 14 days later

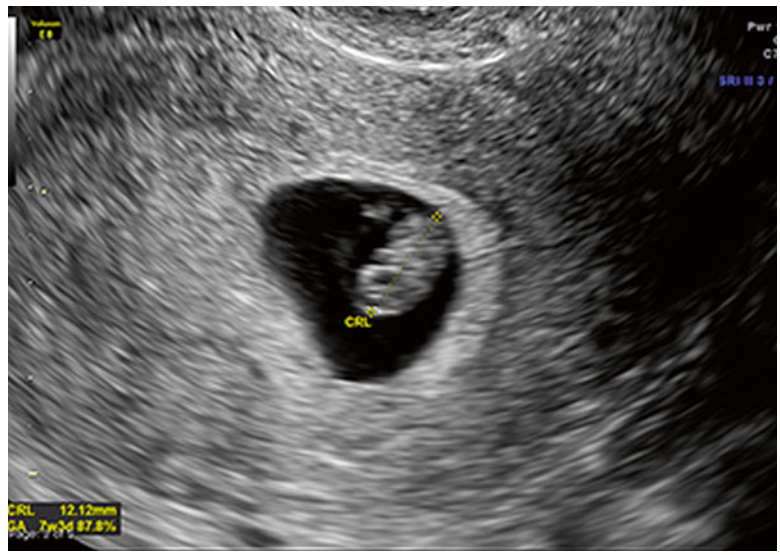

Fig. 10.5 Nonviable pregnancy. CRL = 12.2 mm, with no cardiac activity on initial evaluation

would be encountered (Fig. 10.4). The lack of fetal cardiac activity with a crown-rump length (CRL) = 4 or 5 mm had a false-positive rate of 8.3 %. There were no false-positive results using a CRL cutoff of 5.3 mm. However, considering the identified variability, they recommended using a CRL ≥ 7 mm as the cutoff for determining a nonviable pregnancy (Fig. 10.5). It was recommended that observation with a repeat ultrasound in ~7 days was appropriate in hemodynamically

stable patients who did not warrant the more stringent cutoffs identified by their study.

In 2013, a multispecialty panel on early first trimester pregnancy diagnosis was convened to review the literature and make further recommendations [7]. This panel's goal was to virtually eliminate false-positive results for early pregnancy failure, thus preventing intervention in early viable intrauterine pregnancies. They had similar findings as Abdallah's, recommending cutoffs of ≥2.5 cm for MSD without an embryo, and 7.0 mm without embryonic cardiac activity for defining a nonviable pregnancy. In addition, ultrasound findings diagnostic for pregnancy failure included the absence of an embryo with cardiac activity ≥11 days after demonstrating a gestational sac with a yolk sac, or ≥14 days after demonstrating a gestational sac without a yolk sac (Table 10.2; Fig. 10.6). They also established criteria that were suspicious, but not diagnostic, of a failed pregnancy (Table 10.3).

Table 10.2 Ultrasound findings *diagnostic* of pregnancy failure [7]

• Crown-rump length of ≥7 mm without cardiac activity
• Mean sac diameter of ≥25 mm without an embryo
• Absence of embryonic cardiac activity ≥11 days after an ultrasound showing a gestational sac with a yolk sac
• Absence of embryonic cardiac activity ≥14 days after an ultrasound showing a gestational sac without a yolk sac

Summary

Transvaginal sonography has remarkable improved our assessment of early pregnancy. Recent studies have altered our understanding of the ultrasound findings associated with early intrauterine pregnancies, as well as early pregnancy failure. Adopting these revised guidelines will reduce inappropriate treatment of early intrauterine pregnancies with methotrexate, and avoid intervening on early intrauterine pregnancies destined for viability.

Table 10.3 Ultrasound findings suspicious for pregnancy failure [7]

• Crown-rump length of <7 mm without cardiac activity
• Mean sac diameter of 16–24 mm without an embryo
• Absence of embryonic cardiac activity 7–10 days after an ultrasound showing a gestational sac with a yolk sac
• Absence of embryonic cardiac activity 7–13 days after an ultrasound showing a gestational sac without a yolk sac
• Absence of an embryo >6 weeks after a sure last menstrual period
• Empty amnion with no visible embryo
• Enlarged yolk sac (>7 mm)
• Small gestational sac in relation to the size of the embryo
– Defined as <5 mm difference between the MSD and the CRL

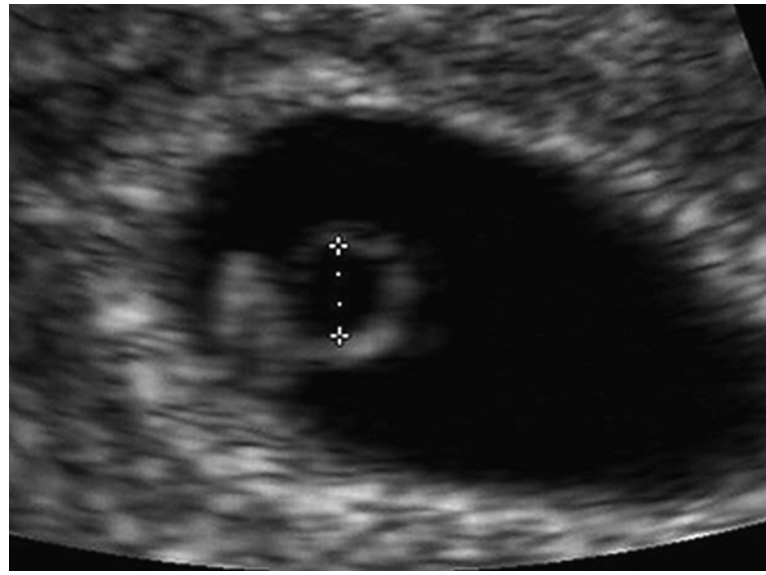

Fig. 10.6 Embryo (*arrow*) with cardiac activity visualized 10 days after visualizing a yolk sac with no embryo

Teaching Points

- The threshold hCG value for initial visualization of an intrauterine pregnancy ranges between 390 and 1000 mIU/mL.
- The discriminatory value (that level where all intrauterine pregnancies should have an identifiable gestational sac) in identifying an intrauterine pregnancy is higher than previously advocated. It is recommended to raise the discriminatory level of hCG to at least 3000 mIU/ml.
- The discriminatory level of hCG is higher with multiple pregnancies. Thus, additional caution should be exercised in patients who have undergone assisted reproduction to conceive.
- Findings that confirm pregnancy failure include:
  - The lack of a fetal heartbeat with a crown-rump length ≥7 mm.
  - A mean sac diameter of ≥25 mm with no embryo.
  - Absence of an embryo with a heartbeat ≥2 weeks after an ultrasound revealed a gestational sac without a yolk sac.
  - Absence of an embryo with a heartbeat ≥11 days after an ultrasound revealed a gestational sac with a yolk sac.

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The Fetal Heart in Early Pregnancy

11

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and Manasi S. Patwardhan

Introduction

Congenital heart defects (CHD) are the most common fetal structural anomalies, either in isolation or in association with other fetal anatomical defects [1, 2]. CHD is strongly associated with chromosomal anomalies and genetic syndromes and can significantly change the clinical surveillance plan and perinatal outcome of affected fetuses [3–7]. Most cardiac defects can be detected early in pregnancy, while some may present later in gestation. The prevalence of major cardiac defects reported varies in literature from 3 to 12 per 1000 pregnancies [8, 9]. This variation is mainly due to the number of minor defects included across different studies [10]. In the pre-echocardiography era, reported incidences ranged from 5 to 8 per 1000 live births. Better imaging techniques and technology have enabled more accurate detection of minor cardiac defects; thus, current estimates range from 8 to 12 per 1000 live births, with some minor geographic variations in the types of congenital heart disease [1].

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Basic Description of Cardiac Development[1]

Formation of the fetal heart begins at around 23–25 days of gestation when the embryo is 2 mm long and it is completed at approximately the 46th day, when most of the cardiac structures are already formed, at an embryonic length of 17 mm. Some structures, such as the atrioventricular septum, can complete their development later in pregnancy. The fetal heart starts contracting at approximately 23 days of gestation. Four main processes occur during the development of the fetal heart: (1) formation of the cardiac tube, (2) looping of the heart, (3) formation of the cono-truncus, and (4) septation. In each of these processes, specific cardiac defects can originate [11–13].

At 23–25 days of gestation (2-mm embryo), clusters of angiogenic cells, called *blood islands*, create a vascular plexus in the anterior segment of the embryo. These clusters generate two primitive cardiac tubes which will later fuse, forming the *bulboventricular tube*; the primitive ventricles and the outflow tracts originate from this structure. At this stage, the aortic sac and aortic arches begin to develop, and the process of cardiac looping is initiated through bending of the cardiac tube towards the anterior and right parts of the embryo. One of the main cardiac defects

[1] See also Chap. 4.

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originating at this stage is transposition of the great arteries.

On gestational day 28 (3-mm embryo), the early embryonic ventricle originates from the diverticula located near the left ventrolateral border of the cardiac tube. These diverticula penetrate the myocardium, increasing its thickness and creating multiple trabeculae which form the *primitive left ventricle*. The *bulbus cordis* splits into three sections: the proximal third forms the *primitive right ventricle*; the middle third forms the *conus cordis* and the outflow portions of the ventricles; and the terminal third forms the aortic and pulmonary roots or primitive *truncus arteriosus*. The formation of the primitive atria, and the septum primum and septum secundum, as well as the process of septation begins at this stage. Cardiac defects that can develop during this period are single ventricle, double inlet and double outlet right ventricle, atrial septal defects and truncus arteriosus.

On gestational days 29–30 (4- to 5-mm embryo), the *sinus venosus* and the *sinus cordis* are formed and the external shape of the heart resembles a 4-chamber structure. Cardiac defects that can occur during this period are: persistent left superior vena cava, Tetralogy of Fallot, and ventricular septal defects.

On gestational days 30–32 (5- to 6-mm embryo), the atrioventricular canal, the pulmonary veins and septation of the truncus arteriosus are formed. Cardiac defects developing during this period are anomalous pulmonary venous return, persistent atrioventricular canal, ventricular septal and aortico-pulmonary defects, and persistent truncus arteriosus.

Formation of the arterial valves begins on gestational day 36 (9-mm embryo), and of the atrioventricular valves on days 39–40 (10- to 12-mm embryo). Cardiac defects occurring during this period are bicuspid arterial valves, absent arterial valves, tricuspid valve atresia, and Ebstein's anomaly. The development of the aortic arch system is completed at approximately 46 days of gestation (17-mm embryo). Cardiac defects developed during this period are double aortic arch, interrupted aortic arch, right aortic arch, and coarctation of the aorta.

Detection of Fetal Congenital Defects

One of the most important contributions of ultrasound (US) in obstetrics is the identification of fetal structural anomalies [14–17]. Although the sensitivity of ultrasound as an imaging technique is completely dependent on the operator's experience and technical skills, other factors such as demographics of the population, gestational age at examination, type of ultrasound equipment, and number of ultrasound scans performed during pregnancy can modify the detection rate of fetal congenital anomalies.

The systematic evaluation of the fetal heart in the mid trimester of pregnancy was first proposed by Allan et al. [18–20] during the early 1980s. Prior to this period, the fetal heart was visualized only in very specific high-risk conditions and towards the end of pregnancy [21, 22]. The main limitations were the poor image resolution of the ultrasound systems, the lack of standardization for fetal evaluation, and the lack of or reduced experience in prenatal diagnosis of congenital heart defects. During the last 30 years, technological advancements in ultrasound systems and most importantly, adequate training of operators and the proposal of standard protocols for fetal evaluation have greatly increased the detection rate of all fetal anomalies, including those in the fetal heart [23–25]. Various ultrasound organizations have proposed guidelines for systematic evaluation of the fetal heart and standards for achieving an adequate detection rate [26, 27]. The optimal period in pregnancy for evaluation of the fetal heart is between 22 and 24 weeks of gestation [28] and that for an early cardiac examination is between 11 and 13 + 6 weeks of gestation [29, 30]. Still, some fetal cardiac anomalies can present in later gestation [31–33]. Technical advances in high-frequency ultrasound probes and the complementary use of 3D and 4D ultrasound techniques have also contributed to an increase in our knowledge of cardiac structure, function, and progression of disease in early stages of pregnancy [34–36].

Why Do We Have to Scan the Fetal Heart Early in Pregnancy?

The most frequent indications for early fetal cardiac evaluation are: family history or obstetric history of congenital heart defects [37, 38]; fetuses with abnormal cardiac images during the first trimester scan [39]; indirect markers for fetal congenital heart defects such as: increased nuchal translucency [40–42], abnormal flow in the ductus venous [43–46], tricuspid regurgitation [47], cystic hygroma [48, 49], and fetuses presenting with any other structural defect [50, 51]. Monochorionic twin pregnancies [52] and pregnancies by assisted reproductive techniques [53] may also benefit from an early cardiac examination as these pregnancies have a higher risk of congenital heart defects (Table 11.1). Cardiac anomalies that can be treated in utero such as aortic stenosis may benefit from an early cardiac examination [54]. In families with a previous history of congenital heart disease, a normal cardiac examination can provide reassurance and reduce the stress and anxiety of their past experience [55].

Table 11.1 Risk factors associated with the presence of congenital heart defects (CHD)

Indication	Association with cardiac defects (%)
Other structural anomalies [103]	21
Increased nuchal translucency [104]	7
Tricuspid regurgitation [47]	5.1
Previous history of CHD [37]	8.7
Abnormal ductus venosus [105]	7.5
Monochorionic twins [52]	5.5 (9.3 in cases with TTS)
Aberrant right subclavian artery [75]	5.1
Assisted reproductive techniques [53]	4.3
Consanguinity [106]	4.4

What Constitutes a Normal Early Fetal Cardiac Examination?

Demonstration of normal situs, cardiac connections, atrioventricular junction, right- and left-sided symmetry and septo-aortic continuity are constituents of a normal early cardiac examination [56]. However, in order to conclude that the fetal heart appears normal, the following parameters should be evaluated.

Heart-to-Chest Ratio

Although the heart size continues to increase with gestational age [57], the mean heart-to-chest area ratio of 0.20+−0.04 is constantly maintained between 11 and 14 weeks [58].

Cardiac Axis

The complex process of cardiac looping during embryonic development is demonstrated by the cardiac axis being fairly midline at 8 weeks and then gradually levo-rotating by 12 weeks after which it stabilizes at the end of the first trimester [59]. Fetuses with cardiac defects might show an abnormal deviation of the cardiac axis in relation to gestational age [60]. Mc Brien et al. [59] studied the normal changes in the fetal cardiac axis between 8 and 15 weeks of gestation and reported that the cardiac axis is orientated more to the midline of the thorax in early gestation, and then rotates to the left with advancing gestation. The authors noted that the cardiac axis changed from 39° at 11 weeks to 50° at 14 weeks. Sinskovskaya et al. [60] reported a normal variation in the cardiac axis from 34.5° at 11 weeks to 56.8° at 13+6 weeks of gestation, and that an abnormal cardiac axis in early gestation can be associated with coarctation of the aorta, Ebstein's anomaly, transposition of the great vessels and heterotaxy. The same group recently showed that 74.1 % of fetuses with confirmed congenital heart defects had an abnormal cardiac axis when evaluated between 11 and 14+6 weeks/days of gestation [61].

Cardiac Planes (Table 11.2)

Marques Carvalho et al. [62] explored the feasibility of obtaining the 4-chamber view and outflow tracts with transvaginal ultrasound in early pregnancy. The authors obtained the three planes in 37 % of fetuses at 11 weeks of gestation, and in 85 % of fetuses at 12 weeks of gestation. At 14 weeks, the three planes were obtained in 100 % of fetuses. The required time for examination at 14 weeks did not exceed 20 min. The authors concluded that after a crown-to-rump length of 64 mm, obtaining these three cardiac planes was completely feasible.

Carvalho et al. [56] suggested that the routine examination of the fetal heart at 11–13+6 weeks should include the following: the visceral situs solitus, cardiac position (axis), normal and symmetric 4-chamber view, two separate atrioventricular valves, normal aortic and pulmonary outflow tracts, two great arteries of similar size, and evidence of aortic and ductal arches. The authors mentioned that septal defects cannot be completely excluded, and that evolving cardiac lesions might not be visible in early pregnancy. Krapp et al. [63] reported that during the 11–13+6 week scan, the 4-chamber view could be visualized in 96 % of fetuses, the left ventricular outflow tract in 97 %, the 3-vessel view in 98 %, and the aortic arch in 72 % of fetuses, whereas the pulmonary veins were observed in 23 % of cases. Yagel et al. [64] proposed the following planes for fetal heart examination: upper abdomen, 4-chamber view, 5-chamber view, bifurcation of the pulmonary artery, 3-vessel and trachea, and the short axis of the right ventricle. The transvaginal route was suggested to be better than transabdominal ultrasound for detailed examination of the fetal heart. The authors reported that all proposed cardiac planes were obtained in 98 % of fetuses at 11–12 weeks, and in 100 % of fetuses at 13–15 weeks of gestation. They reported a 64 % detection rate for CHD when the cardiac examination was performed before 15 weeks of gestation and an extra 17 % detection when the heart was reevaluated at 20–24 weeks, with an overall detection rate of 85 % for CHD. Khalil et al. [65] proposed the following steps for cardiac evaluation in early pregnancy: assessment of the fetal position, orientation of the fetal heart, visualization of the 4-chamber view, assessment of the tricuspid valve and tricuspid regurgitation, visualization of the outflow tracts, and identification of the aortic and pulmonary arches. Abu-Rustum et al. [24] reported the following success rate for visualization of the cardiac structures during an early fetal cardiac scan: 4-chamber view (100 %), presence/absence of tricuspid regurgitation (100 %), crossing of the great vessels (90 %), bifurcation of the pulmonary artery (81 %), 3-vessel view (55 %), aortic arch (76 %), superior and inferior venae cavae (65 %), and ductus venosus (99 %). They also suggested that operators should perform a minimum of 70 fetal heart examinations at 11–13+6 weeks to gain reliable experience for obtaining the proposed anatomical planes with an allocated time of up to 10 min for fetal cardiac evaluation.

Operator Experience and Route of Ultrasound Examination

Allan [66] suggested that experience and technological resources are the main factors associated with differences in the detection rate of CHD, when transvaginal and transabdominal ultrasound examinations are compared. She suggested that

Table 11.2 Visualization of fetal cardiac structures during the early ultrasound fetal cardiac examination at 11–13+6 weeks of gestation

	10 weeks	11 weeks	12 weeks	13 weeks	13+6 weeks
4-chamber view	Yes	Yes	Yes	Yes	Yes
Outflow tracts	No	No	Yes	Yes	Yes
Aortic and ductal arch	No	No	Yes	Yes	Yes
Superior and inferior venae cavae	No	No	Yes	Yes	Yes
Pulmonary veins	No	No	No	Yes	Yes

the success of transabdominal examination can be attributed to the participation of a pediatric cardiologist in the scanning process, whereas transvaginal studies are mainly performed by obstetricians with limited experience in cardiac scanning. She concluded that it is not enough to only obtain the cardiac planes, but to also have the proper knowledge to interpret the images; and that another important factor for improving the detection of cardiac anomalies is the development of technical skills to improve the scanning plane, either by adjusting the position of the US probe or by changing the position of the mother [66]. Tegnander et al. [67] evaluated the detection of fetal cardiac anomalies by comparing operators with different levels of experience. Sonographers with previous experience of more than 2000 examinations had a 52 % detection rate of CHD as compared with a 32.5 % detection rate of operators previously performing fewer than 2000 cardiac examinations. This difference remained unchanged between the two groups of sonographers when detection of isolated CHD, or CHD with associated anomalies was analyzed. The authors concluded that it is necessary to become proficient in the visualization and interpretation of the 4-chamber view and of the left and right ventricular outflows before obtaining other anatomical cardiac planes. They suggested that, despite using a state-of-the art ultrasound system and/or the combination of different ultrasound techniques, operator experience still remains the key factor in improving the detection rate of CHD.

Well-trained operators can achieve a good detection rate of CHD early in pregnancy. Hartge et al. [68] studied a group of 3521 pregnant women presenting with 77 (2.1 %) fetuses with CHD. The ultrasound scans were performed by highly trained operators, using state-of-the art ultrasound systems with high frequency transvaginal probes. They reported 85.7 % detection rate of cardiac anomalies at 11–13 + 6 weeks of gestation. The authors mentioned that, in 64.2 % of cases, only the transabdominal route for ultrasound evaluation was needed and, in the remaining 35.8 % of patients, both transabdominal and transvaginal routes were used. The authors reported that conditions such as coarctation of the aorta, hypoplastic left heart resulting from aortic stenosis, and Tetralogy of Fallot might not be identified early in pregnancy. They concluded that well trained operators and high technology US systems are necessary to achieve a high detection rate of CHD in early pregnancy.

Rasiah et al. [69] performed a systematic review of the diagnostic performance of fetal echocardiography in the first trimester of pregnancy. They identified ten studies done in tertiary centers with good quality control that met the inclusion criteria. They reported a combined sensitivity of 85 % (95 % CI, 78–90 %) and specificity of 99 % (95 % CI, 98–100 %), positive likelihood ratio (LR) of 59.6 (95 % CI, 26.5–133.6), and negative LR of 0.25 (95 % CI, 0.1–0.6) for identification of congenital heart defects. The authors mentioned that, although transvaginal ultrasound is thought to be a better modality for visualization of the fetal heart, the training and experience of the operators and high quality US systems can lead to similar detection rates using transabdominal ultrasound.

When Is the Optimal Time to Perform Early Fetal Cardiac Evaluation?

Carvalho et al. [56] suggested, aside from operator experience, gestational age at examination is an important factor associated with a successful evaluation of the fetal heart. Haak et al. [70] reported that at 11 weeks successful evaluation of the heart can be achieved in about 20 % of fetuses, whereas at 13 weeks of gestation the success rate for fetal cardiac evaluation increases to 92 %.

Smrcek et al. [71] studied fetuses from 10 to 15 weeks of gestation to evaluate the following cardiac planes: 4-chamber view, 3-vessel view, origin and crossing of the great arteries, aortic and ductal arches, superior and inferior venae cavae, and at least two pulmonary veins. They were able to identify all structures at 10 weeks of gestation, except for the superior and inferior

vena cava, which were visualized at 11 weeks. The pulmonary veins were observed in 80 % of fetuses between 12 and 14 weeks, and in 100 % of fetuses at 15 weeks of gestation. The authors reported an increment in the detection rate of cardiac defects, from 67 % at 10 weeks to 100 % at 15 weeks of gestation. They mentioned that, between 10 and 13 weeks, the transvaginal route for ultrasound examination was better than the transabdominal route; that, between 12 and 14 weeks of gestation, both transabdominal and transvaginal ultrasound had a similar detection rate; and from 15 weeks of gestation onward, the transabdominal route was better. The authors mentioned that complementary use of color directional Doppler and power Doppler, and not limiting the scanning time, can improve the optimal visualization of the fetal heart.

Vimpelli et al. [72] evaluated the feasibility of performing the cardiac examination at different weeks during the first trimester of pregnancy. The authors aimed to obtain the following planes: 4-chamber, longitudinal views of the aorta and pulmonary trunks, crossing of the great arteries, and aortic and ductal arches. The authors reported that visualization of all structures varied from 43 % at 11 weeks to 62 % at 13+6 weeks. The 4-chamber view was obtained in 74 % of cases at 13+6 weeks. McAuliffe et al. [73] evaluated a high-risk group of 160 women, defined by previous history of congenital heart disease, increased nuchal translucency, or the presence of a non-cardiac malformation during the nuchal scan. The authors evaluated the following cardiac parameters: 4-chamber view, symmetry of the cardiac chambers, atrioventricular valves, outflow tracts, crossing of the great arteries, and, when possible, the ductal and aortic arches. The mean gestational age at examination was 13.5 weeks, and the prevalence of cardiac defects was 12.5 % ($n=20$). The 4-chamber view was seen in 100 % of fetuses, the tricuspid and mitral valves in 96 %, the outflow tracts in 95 %, the aortic and ductal arches in 45 %, and the pulmonary veins in 16 %. From 20 fetuses with CHD, 14 (70 %) were identified during the first trimester scan; the authors reported a specificity of 98 %, a positive predictive value (PPV) of 87.5 % and a negative predictive value (NPV) of 96 %.

Indirect Markers for Early Fetal Cardiac Evaluation

Borrell et al. [43] analyzed the contribution of increased nuchal translucency, tricuspid regurgitation, and reversed A wave in the ductus venosus in the identification of fetal cardiac defects in chromosomally normal fetuses. They reported that, among fetuses identified at 11–14 weeks with congenital heart disease, 40 % also had increased nuchal translucency, and 39 % had reversed A wave in the ductus venosus.

Clur et al. [74] reported that increased nuchal translucency, abnormal ductus venosus, and tricuspid regurgitation were the most frequent extra-cardiac ultrasound findings related with congenital heart disease. They showed that fetuses with normal chromosomes, but with increased nuchal translucency and reversed A wave in the ductus venosus, had an 83 % prevalence of cardiac defects. The authors also proposed that analysis of the pulsatility index of the ductus venosus, instead of presence/absence of atrial flow, might increase to 70 % the detection rate of fetal cardiac anomalies.

Pereira et al. [47] studied 85 euploid fetuses with major congenital heart defects and found an increased nuchal translucency (>95th percentile) in 35.3 %, tricuspid regurgitation in 32.9 %, and reversed A wave in the ductus venosus in 28.2 % of fetuses during first trimester ultrasound screening. In fact, any one of these markers was identified in 57.6 % of fetuses with cardiac defects and in 8 % of structurally normal fetuses. They concluded that these three markers improved the performance of screening for congenital heart defects in the first trimester.

Rembouskos et al. [75] suggested an association between aberrant right subclavian artery (ARSA) and fetal cardiac defects. The authors studied 4566 fetuses and identified 89 fetuses with ARSA, of which 12 fetuses had a chromosomal anomaly. The prevalence of fetal cardiac defects in chromosomally normal fetuses with ARSA was 4/77 (5.1 %), including Tetralogy of Fallot ($n=1$), aberrant umbilical vein ($n=1$) and tricuspid atresia ($n=2$). The authors suggested that early fetal echocardiography is indicated in the presence of ARSA.

Sinkovskaya et al. [60, 61] evaluated the performance of cardiac axis measurement in early gestation for detection of major fetal cardiac defects. They examined the cardiac axis between 11 and 14 + 6 weeks in fetuses with confirmed congenital heart defects across three tertiary centers. They documented an extreme left or right deviation of the cardiac axis in 74.1 % of fetuses with congenital heart defects. In their study the cardiac axis performed better than enlarged nuchal translucency, tricuspid regurgitation, or reversed A wave in the ductus venosus, alone or combined, in detecting major fetal cardiac defects.

Clinical Application: Imaging the Fetal Heart in Early Pregnancy, Practical Recommendations

It is necessary for the operator to adjust the settings of the ultrasound system prior to a fetal cardiac examination. Even though this is an individual process, some basic principles might contribute to improved image quality.

Frequency and Depth

High-frequency transducers are a better option if the fetal heart is located close to the ultrasound probe. Transvaginal high-frequency ultrasound probes emitting at 9–12 MHz might be preferable at 11–12 weeks of gestation when the fetus is located close to the probe, whereas probes emitting at 5–9 MHz might be preferred at 12–13 weeks of gestation when the fetus is located away from the transducer. Transabdominal examination might be better with a linear 9-MHz probe if the fetus is located close to the maternal abdominal wall; if not, a 2- to 5- or 4- to 6-MHz probe might provide better ultrasound images. During B-mode, system settings should be optimized to obtain images with a high frame rate, increased contrast and high resolution along with the use of low persistence, a single acoustic focal zone and a relatively narrow image field. Depth adjustment and magnification should be employed when possible. Harmonic imaging can also be used to improve image quality and particularly for patients with increased maternal abdominal wall thickness.

Identification of the Scanning Planes

Transvaginal ultrasound might provide adequate images when performed between 11 and 12 weeks of gestation and when the fetus is in an optimal position. In some cases the required planes might not be immediately acquired, as the possibility of modifying the position of the uterus and the fetus and manipulating the ultrasound probe is limited. A prolonged transvaginal examination might be uncomfortable. In patients with increased body mass index, or with previous cesarean section or abdominal surgery, the transvaginal route for fetal cardiac examination should be preferred. Transabdominal examination from 13 weeks onwards offers the possibility to freely manipulate the ultrasound probe, and to change the position of the patient and of the scanning bed to acquire the fetal cardiac planes. The scanning time can also be prolonged.

A cross sectional plane of the fetal thorax with the heart in an apical projection and the fetal spine in the lower part of the ultrasound screen is the optimal image for cardiac examination. The 4-chamber view, 5-chamber view, crossing of the big arteries, and 3-vessel view can be obtained from this projection by performing a slow sweep towards the fetal head and maintaining cross sectional images of the studied planes (Fig. 11.1). The two outflow tracts can be visualized by rotating the ultrasound probe clockwise or anticlockwise from the 4-chamber view (Fig. 11.2). By rotating the probe 90° from the 4-chamber view, a sagittal plane of the thorax is obtained, and by gently moving the ultrasound probe from side to side, the aortic and ductal arches, and inferior and superior vena cava can be observed (Fig. 11.3). Color directional Doppler might be helpful in assessing the integrity of the interventricular septum, to visualize the crossing of the great arteries,

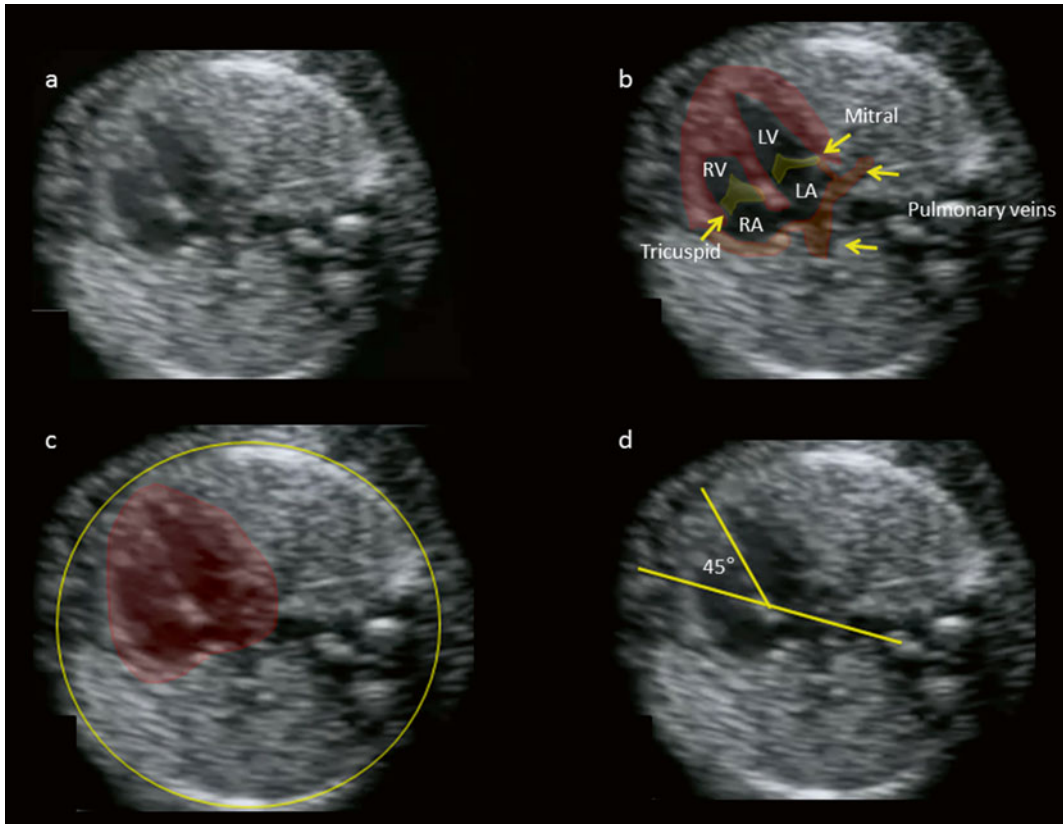

Fig. 11.1 Cross-sectional image of the fetal heart at the level of the 4-chamber view at 13 + 5 weeks /days of gestation. (**a**) 4-chamber view. (**b**) Highlighted anatomical structures: *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle. Note the pulmonary veins reaching the left atrium. (**c**) Heart-to-thorax ratio. (**d**) Cardiac axis

and to document the direction of flow in the aortic arch (Fig. 11.4). Spectral Doppler is probably not necessary at this stage unless evaluation of the fetal cardiac function is necessary.

Clinical Application: Detection of Cardiac Anomalies

There is a great variation in the detection rate of congenital heart disease due to non-modifiable factors, such as: the prevalence of the disease, the presence of high-risk ultrasound markers, the type of CHD and some modifiable factors, such as: the population screened, gestational age selected at scanning, operator experience and ultrasound system and techniques used (Table 11.3).

Low-Risk Population

Volpe 2011 et al. [76] studied 4445 low risk fetuses with a 0.9 % prevalence of cardiac defects ($n = 42$), 28 major and 14 minor. A total of 39 cases were identified prenatally, 29 (69 %) during the first-trimester scan and 10 (23.8 %) in later stages of pregnancy. The authors mentioned that increased nuchal translucency, tricuspid regurgitation and reversed A wave in the ductus venosus were associated with a higher prevalence of fetal cardiac defects. The presence of these ultrasound markers should be considered an indication for targeted fetal cardiac evaluation. The authors reported that an abnormal 4-chamber view had a 50 % detection rate for major cardiac defects (Figs. 11.5 and 11.6).

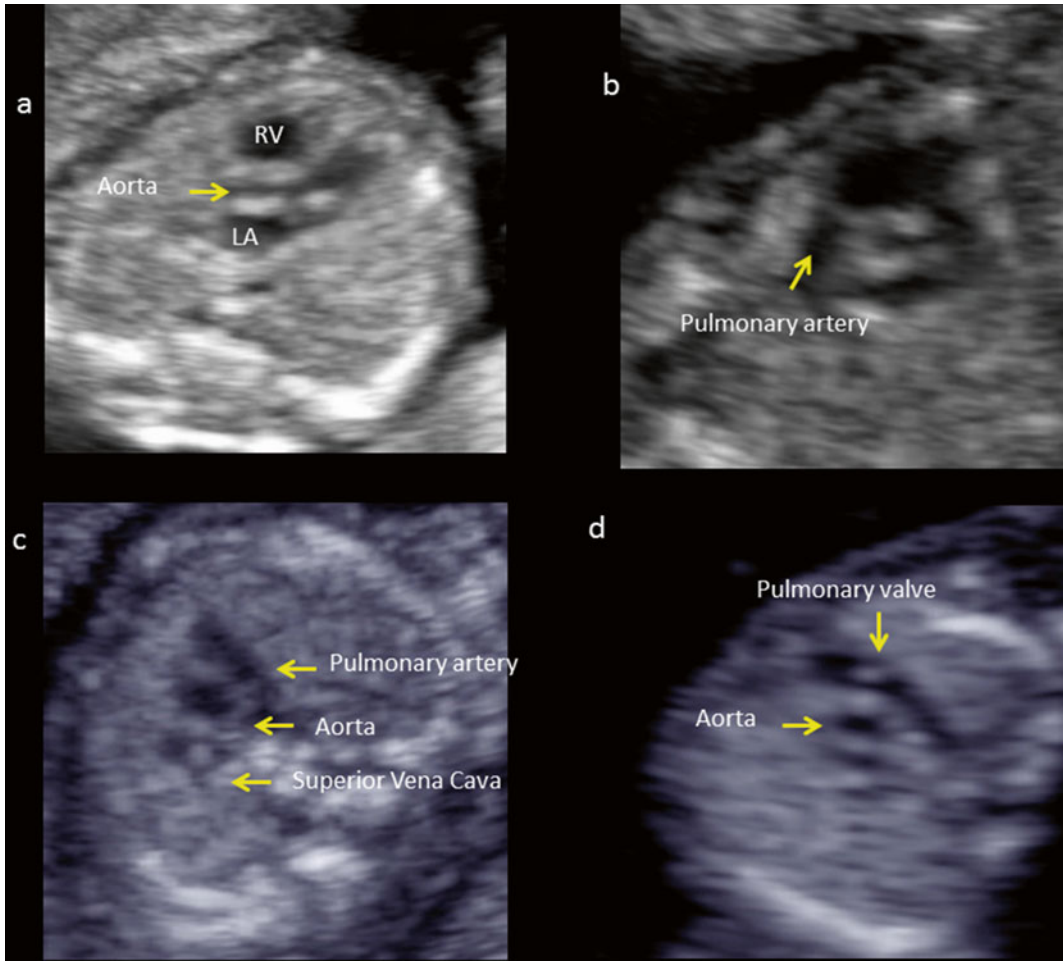

Fig. 11.2 Outflow tracts and 3-vessel view. (**a**) Left outflow tract and aorta (*LA* left atrium, *RV* right ventricle). (**b**) Right outflow tract and pulmonary valve obtained from a short axis. (**c**) 3-vessel view. (**d**) Slightly oblique plane from the 3-vessel view to obtain the pulmonary valve

Iliescu et al. [77] evaluated 5472 unselected patients and reported a prevalence of cardiac defects of 0.54 % ($n=30$). Early examination of the fetal heart detected 40.6 % of congenital heart defects, 75 % of them major. The authors mentioned that 89 % of minor cardiac defects were detected in late stages of pregnancy. The authors confirmed that increased nuchal translucency had a strong association with fetal cardiac defects; 8.68 % of fetuses with increased nuchal translucency had major cardiac anomalies, and 96 % of them were detected during the first trimester cardiac scan. First trimester echocardiography was able to similarly identify major CDH in fetuses with increased or normal nuchal translucency. The authors reported that the time required for first trimester examination ranged from 18 to 52 min (median, 34 min).

Rossi and Prefumo [78] performed a systematic review of the evaluation of the fetal heart in the first trimester of pregnancy in a low risk population. The overall diagnostic performance at 11–14 weeks for detection of congenital heart defects was 48 % (210/418). The authors mentioned that the addition of Doppler ultrasound did not improve the detection of CHD. They also

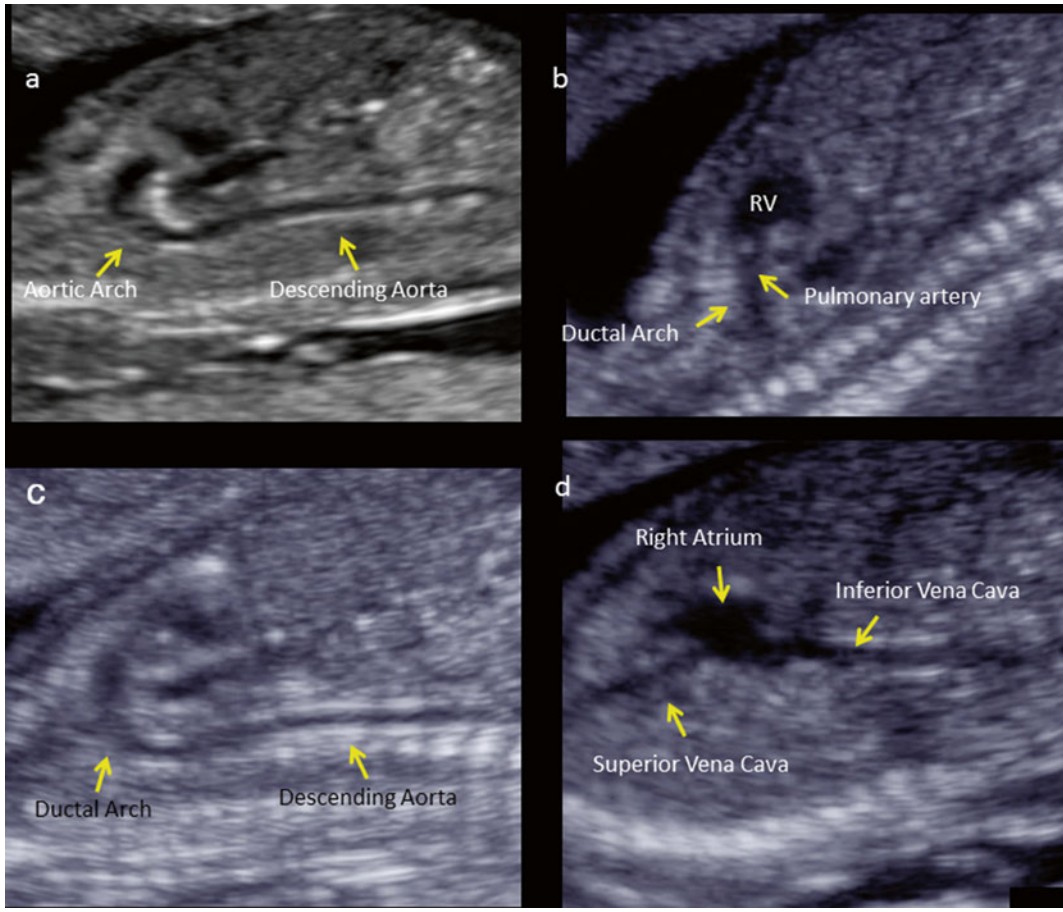

Fig. 11.3 Sagittal images. (**a**) Aortic arch and descending aorta. (**b**) Pulmonary artery and ductal arch (*RV* right ventricle). (**c**) Ductal arch and descending aorta. (**d**) Inferior and superior venae cavae

mentioned that targeted echocardiography in high risk pregnancies was able to identify 53 % of cardiac anomalies, and that an apparently normal fetal cardiac examination at 11–14 weeks does not exclude a cardiac defect.

Hildebrand et al. [79] evaluated a large group of 21,189 unselected pregnant women in Southern Sweden where ultrasound scans were performed by trained midwives. No congenital heart anomalies were detected during the first-trimester scan, and only 5.3 % of congenital heart defects were identified in the second-trimester ultrasound scan. The authors suggested that the operators' lack of experience and non-actualized US systems greatly contributed to the reduced detection rate found in this study.

Syngelaki et al. [80] studied nearly 45,000 patients at 11 and 13+6 weeks of gestation and reported an overall detection rate of cardiac anomalies of 34 %; in particular, they found a 50 % detection rate of hypoplastic left heart (Fig. 11.7), transposition of the great arteries, and double outlet right ventricle; a 33 % detection rate of coarctation of the aorta, Tetralogy of Fallot and atrioventricular septal defects; and no acceptable detection rate for ventricular septal defects, Ebstein's anomaly, aortic and pulmonary stenosis, tricuspid atresia, and cardiac tumors.

Westin et al. [81], in a large multicenter study, also from Sweden, compared the detection rate of cardiac anomalies during the routine fetal examinations, performed between 12 and 18 weeks of

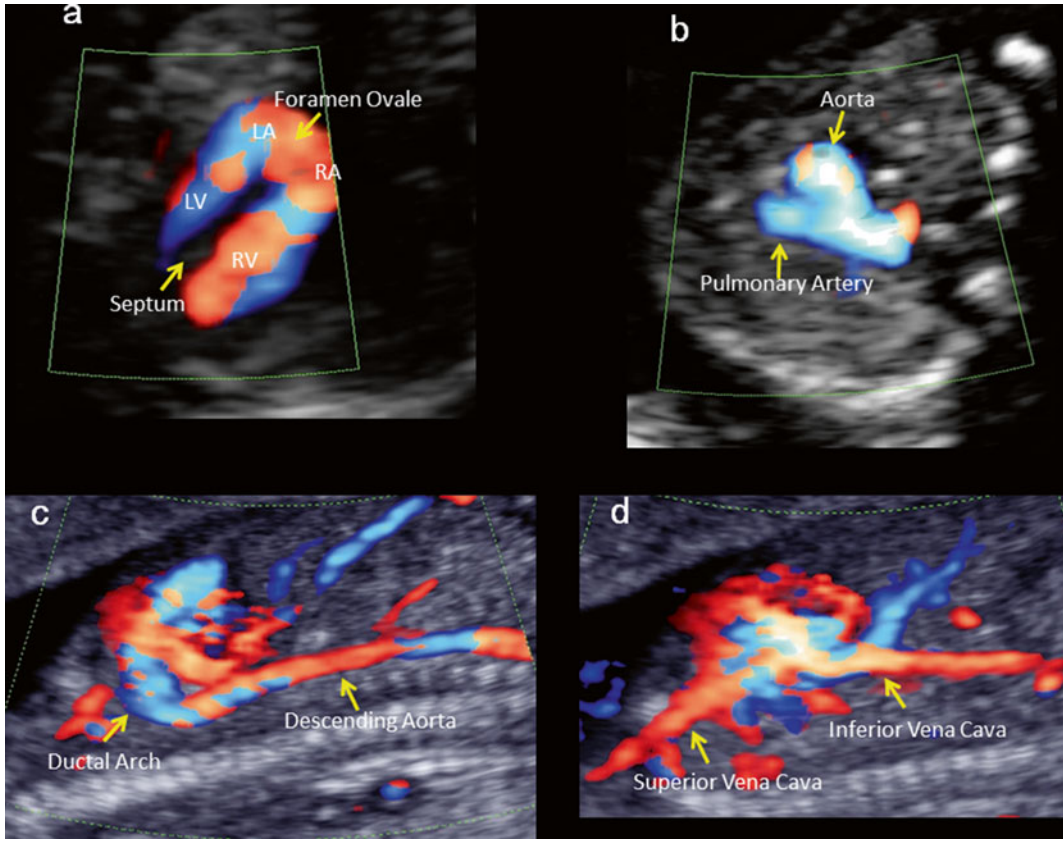

Fig. 11.4 High-definition color directional Doppler. (**a**) Cross-sectional view of the fetal heart and interventricular septum (*LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle). (**b**) Joint of the aorta and pulmonary artery with blood flow moving in the same direction. (**c**) Ductal arch and descending aorta. (**d**) Inferior and superior venae cavae

gestation. The authors reported an 11 % detection rate at 12 weeks and a 15 % detection rate at 18 weeks. The authors mentioned that, using 3.5 mm as a fixed cut-off value for defining an increased nuchal translucency, the detection rate of cardiac defects can be significantly reduced. They also mentioned that differences in operator expertise can be responsible for the low detection rate found in this study.

Eleftheriades et al. [82] studied 3774 fetuses with a prevalence of congenital heart anomalies of 0.77 % ($n=29$) and reported that evaluation of the fetal heart in the first trimester of pregnancy allowed for the diagnosis of almost 45 % of the total number of cardiac defects; 48 % were diagnosed during the 20- to 24-week ultrasound scan, and the remaining 7 % later in pregnancy. The authors also showed a significant association between major cardiac defects and increased nuchal translucency and suggested that the evaluation of the 4-chamber view should be considered as part of the routine fetal examination at 11–13 + 6 weeks of gestation.

High-Risk Population

Persico et al. [83] evaluated the fetal heart in 855 pregnant women undergoing chorionic villus sampling due to the presence of ultrasound markers or altered maternal biochemical markers of fetal chromosomal anomalies. They reported 100 cases in which a cardiac defect was suspected (54 % major and 46 % minor). The authors

Table 11.3 Studies on the diagnostic capacity of early ultrasound for the identification of congenital heart disease

Study	Total (*n*)	Scan route	GA (weeks)	Prevalence of CHD (*n* [%])	Early detection (*n* [%])
Hernadi and Torocsik [107]	3991	TA, TV	11–14	1 (0.02)	–
D'Ottavio et al. [108]	4078	TV	13–14	12 (0.29)	3 (25.0)
Bilardo et al. [109]	1690	TA	10–14	4 (0.23)	–
Hafner et al. [110]	4233	TA	10–14	14 (0.33)	1 (7.1)
Hyett et al. [41]	29,154	TA	10–14	43 (0.15)	1 (2.3)
Schwarzler et al. [111]	4523	TA	10–14	9 (0.20)	–
Mavrides et al. [112]	7339	TA	10–14	24 (0.33)	4 (16.7)
Michailidis and Economides [113]	6650	TA, TV	10–14	9 (0.14)	2 (22.2)
Orvos et al. [114]	4309	TV	10–13	32 (0.74)	–
Taipale et al. [115]	4789	TV	10–16	18 (0.38)	1 (5.6)
Chen et al. [116]	1609	TA, TV	12–14	7 (0.44)	4 (57.1)
Bahado Singh et al. [42]	8167	TA	10–14	6 (0.07)	–
Bruns et al. [117]	3664	?	11–14	9 (0.25)	–
Becker and Wegner [29]	3094	TA, TV	11–14	11 (0.36)	6 (54.5)[a]
Cedergren and Selbing [118]	2708	TA	11–14	3 (0.11)	–
Dane et al. [119]	1290	TA	11–14	1 (0.08)	–
Westin et al. [81]	16,260	TA	12–14	29 (0.18)	–
Muller et al. [120]	4144	TA	10–14	13 (0.31)	–
Chen et al. [121]	7642	TA	10–14	19 (0.25)	7 (36.8)
Oztekin et al. [122]	1805	TA	11–14	2 (0.11)	–
Hildebrand et al. [79]	21,189	?	11–14	62 (0.29)	0
Syngelaki et al. [80]	44,859	TA, TV	11–13	106 (0.24)	36 (34)
Volpe et al. [76]	4445	TA, TV	11–14	28 (0.63)	23 (82.1)
Grande et al. [123]	13,723	TA, TV	11-14	44 (0.32)	25 (56.8)
Hartge et al. [68]	3521	TA, TV	11–13 + 6	77 (2.1)	66 (85.7)
Iliescu et al. [77]	5472	TA, TV	12–13 + 6	30 (0.54)	27 (90)
Persico et al. [83]	886	TA	11–13	100 (11.2)	96 (96)
Eleftheriades et al. [82]	3774	TA	11–13 + 6	29 (0.77)	13 (44.8)
Volpe et al. [100]	870	TA	11–14	62 (0.17)	56 (90.3)
Rossi et al. [78] (systematic review)	78,002	TA, TV	11–14	418 (0.53)	118/224[b] (53)

GA gestational age, *TA* transabdominal, *TV* transvaginal
[a]Only major cardiac defects included
[b]Fetal echocardiography performed in 224

reported a 93.1 % detection rate of cardiac anomalies using transabdominal ultrasound and a high association between congenital heart defects and increased nuchal translucency and tricuspid regurgitation.

Carvalho et al. [84] reported the diagnostic performance of targeted cardiac examination at the end of the first and early second trimesters of pregnancy in 230 high-risk women. Indications for fetal cardiac evaluation were: increased NT, family history of congenital heart disease, and abnormal findings during the routine US scan. They considered a normal US examination when the following structures were visualized: visceral situs solitus, normal cardiac position, normal 4-chamber view, two separate atrioventricular valves, normal aortic and pulmonary outflow tracts, two great arteries of similar size, and visualization of the aortic and ductal arches. The ultrasound scans were mainly performed transabdominally. The authors reported 199 normal and 21 abnormal cardiac evaluations; it was not

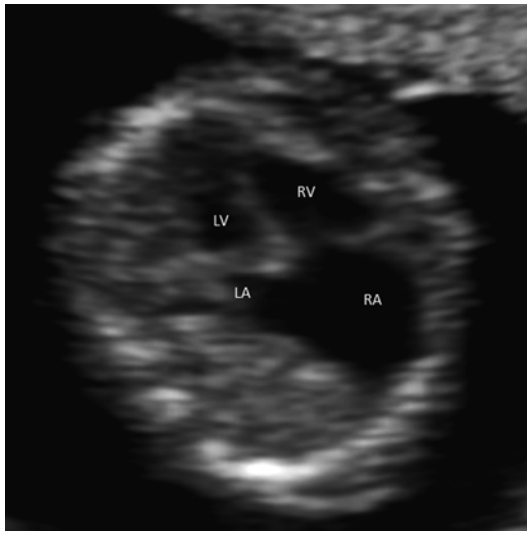

Fig. 11.5 Abnormal 4-chamber view; dilatation of the right atrium due to tricuspid insufficiency

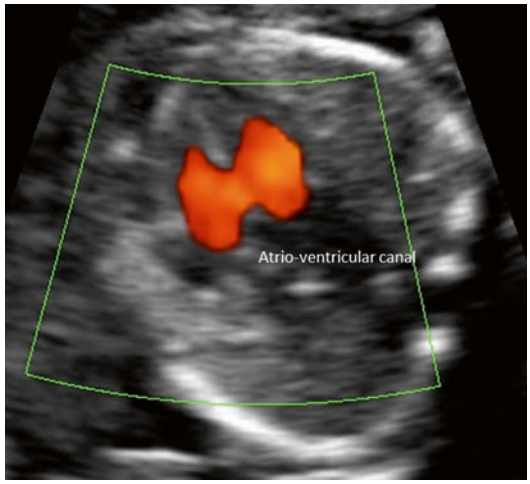

Fig. 11.6 Abnormal 4-chamber view; atrioventricular septal canal (power Doppler ultrasound)

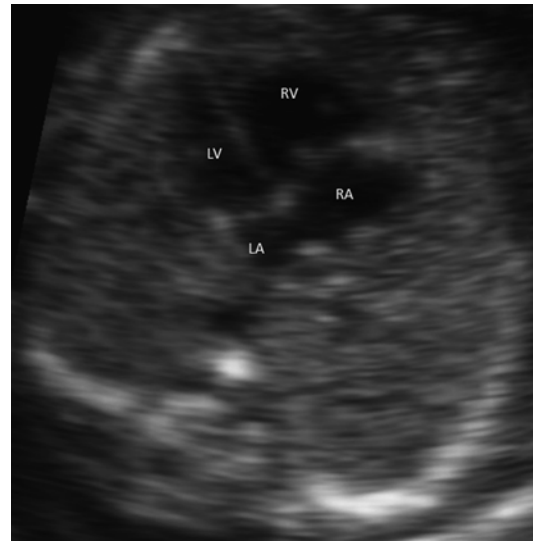

Fig. 11.7 Abnormal 4-chamber view; asymmetric size of the ventricles early manifestation of a hypoplastic left ventricle

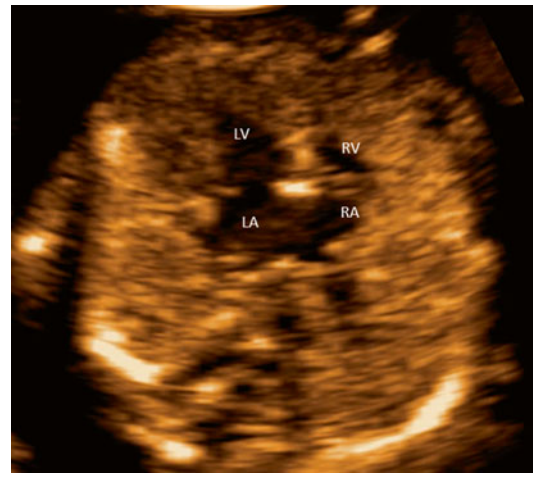

Fig. 11.8 Abnormal 4-chamber view; severely small right ventricle and increased thickness of the left ventricular walls

possible to adequately visualize the heart in ten fetuses. From the 199 normal scans, perinatal results were available in 188 cases, and four of them had a cardiac defect (three ventricular septal defects and one pulmonary stenosis) (Fig. 11.8). From the 21 abnormal scans, 12 fetuses had a major and 2 fetuses a minor cardiac defect. The authors reported a 96 % diagnostic accuracy of early fetal echocardiography in high-risk pregnancies, and a high association between increased nuchal translucency, chromosomal anomalies and cardiac defects.

Becker et al. [29] evaluated 3094 fetuses, referred secondary to an abnormal US examination, or to an increased nuchal translucency and reported a 2.8 % prevalence of CHD ($n=86$), 84.2 % of them detected during the first-trimester fetal cardiac evaluation. The cardiac evaluation

included the visualization of the 4-chamber view, outflow tracts and pulmonary and aortic valves. They reported that fetuses with increased nuchal translucency (>2.5 mm) had a prevalence of heart defects of 9.8 %, whereas fetuses with a normal nuchal translucency (<2.5 mm) had a prevalence of heart defects of 0.3 %.

Smrcek et al. [85] studied 2165 fetuses from low and high risk populations using the combination of 2-D ultrasound image and color directional Doppler. They reported a detection rate for congenital heart defects of 63.0 % (29/46); nine more fetuses (19.5 %) were diagnosed during the second-trimester ultrasound scan. Fetuses with an abnormal cardiac examination had a prevalence of chromosomal anomalies of 65.8 %; a prevalence of abnormal ductus venosus of 51.2 %; and a prevalence of increased nuchal translucency of 32.2 %. The authors mentioned that cardiac defects that tend to progress, such as myocardial hypertrophy, ventricular hypoplasia, fiboelastosis, and coarctation of the aorta, might not be identified at 11–14 weeks.

Improved Detection by Adding Other Ultrasound Findings

Axt-Fliedner et al. [54] reported a case of a normal 4-chamber view at 11 + 3 weeks of gestation with color Doppler indicating increased velocities across the aortic valve. Doppler interrogation across the atrio-ventricular valves and pulmonary outflow was normal. A follow-up ultrasound at 16 + 6 weeks/days demonstrated a hypoplastic left heart with no color flow across the mitral and aortic valve.

Bhat et al. [86] compared diagnosis of fetal Tetralogy of Fallot made before (Group 1) and after (Group 2) 17 weeks of gestation. The main findings increasing the suspicion of Tetralogy of Fallot during early fetal cardiac examination were a more levo rotated 4-chamber view, the presence of ventricular septal defect, overriding aorta, and discrepancy in the size of the great arteries. The authors were able to obtain most of these images early in pregnancy. There were seven out of ten fetuses in Group 1 with pulmonary stenosis and antegrade flow through the ductus arteriosus. Other cardiac anomalies such as interrupted inferior vena cava, bilateral superior vena cava, atrioventricular septal defect, and atrial bigeminy were also documented during the early ultrasound scan. Color Doppler ultrasound contributed to the identification of the outflow tracts. Transabdominal scanning was considered adequate in about 50 % of early ultrasound examinations.

Baschat et al. [87] evaluated four fetuses that were referred for increased nuchal translucency and bradycardia. Fetal heart block was diagnosed using M-mode ultrasound, and a congenital heart defect was present in all four fetuses; three out of four fetuses were confirmed to have heterotaxy on autopsy. Sciarrone et al. [88] identified complex congenital heart defects in two euploid fetuses with increased nuchal translucency and fetal bradycardia during early ultrasound examination.

Lafouge et al. [89] reported a right aortic arch and ductus arteriosus in the first trimester identified by the presence of a mirror image-like appearance of the main vessels in a 3-vessel trachea view.

Prefumo et al. [90] reported two cases of cardiac diverticula with large pericardial effusions. Color flow and Doppler demonstrated bidirectional flow into a saccular dilatation at the ventricular apex filling the pericardial space in both cases.

Complementary Ultrasound Techniques

Fundamental 2D imaging is the cornerstone for fetal cardiac evaluation; color Doppler and M-mode ultrasound might improve the diagnosis of septal defects and cardiac arrhythmias [87, 91]. Four-dimensional (4D)-ultrasound and STIC (Fig. 11.9) can by applied for off-line evaluation of the fetal heart either by the same or by different experts to confirm/exclude congenital heart defects [92].

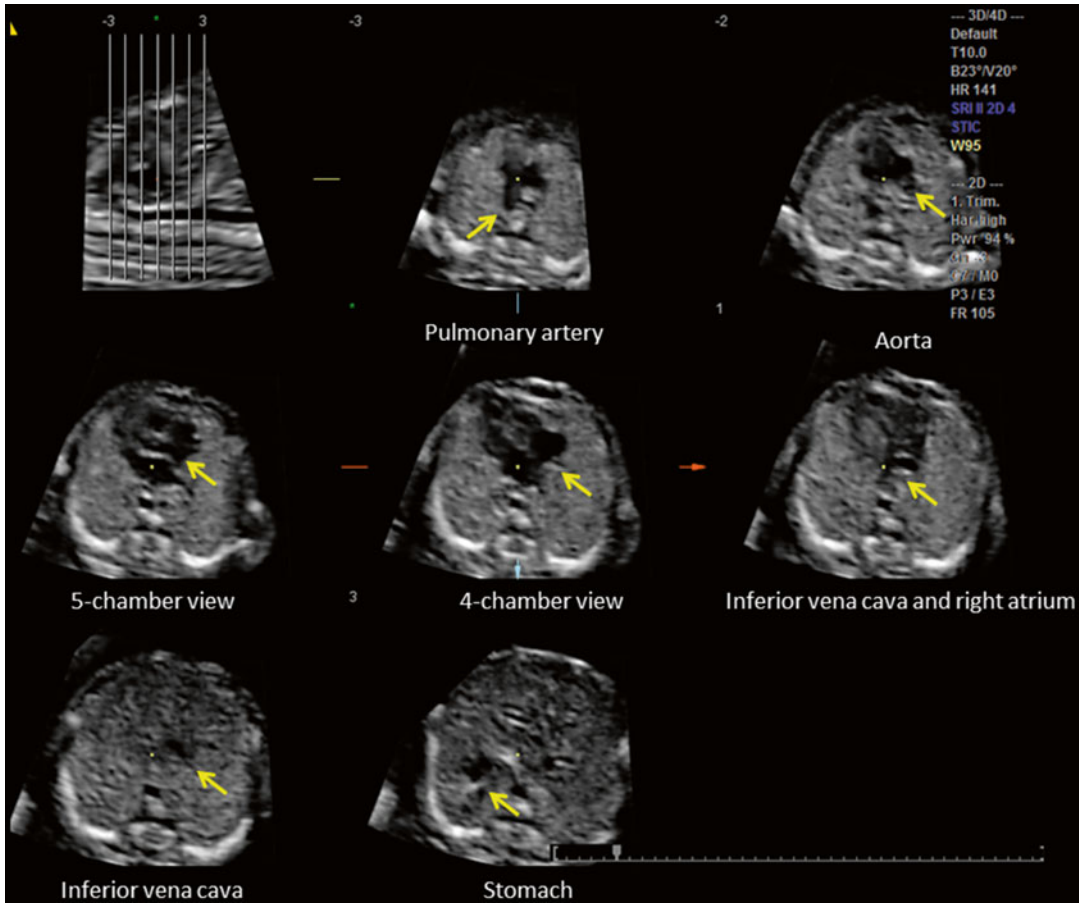

Fig. 11.9 Spatiotemporal imaging correlation (STIC) at 14 weeks of gestation. From a sagittal plane where the ductal arch and descending aorta can be visualized, seven cross-sectional planes are generated using tomographic ultrasound imaging (TUI)

Spatiotemporal Imaging Correlation

Bennasar et al. [93] evaluated the reproducibility in evaluating STIC volumes at 11–15 weeks of gestation for identification of congenital heart defects. The authors used transvaginal ultrasound, combining color directional Doppler and gray-scale images. The structures evaluated in the STIC volume were 4-chamber view, crossing of the great vessels, left and right cardiac outflows, and 3-vessel view. They reported excellent agreement in the visualization of the 4-chamber view and outflow tracts. The same authors also reported that STIC volumes in early pregnancy allowed correct identification of 95 % of fetuses with suspected cardiac anomalies [94].

Espinoza et al. [34] obtained STIC volumes from 16 normal fetuses and 71 fetuses with congenital heart defects. The STIC volumes were evaluated by operators blinded to the clinical diagnosis. The results showed 79 % sensitivity and 90 % specificity for identification of fetal cardiac defects. The authors concluded that acquisition of cardiac STIC volumes and evaluation by an expert in fetal heart can be used to confirm/exclude the presence of a cardiac defect.

Lima et al. [95] explored the combined value of color Doppler ultrasound and STIC volume analysis in the identification of the basic planes for first trimester fetal cardiac examination. The authors reported that this combination allowed identification of most of fetal cardiac planes in

90.6 % of women in STIC volumes obtained either transabdominally or transvaginally. Tudorache et al. [91] also reported excellent reproducibility in obtaining STIC volumes for identification of fetal cardiac structures in early pregnancy.

Turan et al. [96] studied STIC volumes for evaluation of the fetal heart in the first trimester of pregnancy. The authors suggested that good-quality volumes should have the fetal spine clearly seen and minimal or no motion observed in the sagittal view of the multiplanar display of the fetal heart. They were able to visualize the following structures: 4-chamber view, descending aorta, heart size, cardiac axis, two equal size atria and ventricles, two opening atrioventricular valves, two great arteries, crossing and adequate size of the two great arteries, and presence of the aortic and ductal arches with forward flow in both. They reported that the 4-chamber view was obtained in all cases, and the remaining parameters in 85 % of fetuses. Transabdominal ultrasound examination was successful in 92 % of fetuses in obtaining good quality STIC volumes.

Viñals et al. [92] reported the acquisition of STIC volumes in the first trimester of pregnancy and interpretation by an experienced operator located remotely from the acquisition site. They showed that 71 % (35/49) of STIC volumes were obtained within a 20-min period, and a good agreement between operators for identification of fetal cardiac structures was achieved.

Evaluation of the Cardiac Function in Early Pregnancy

The evaluation of the fetal cardiac function in early pregnancies might be a complementary method for improving the identification of congenital heart defects. Clur et al. [74] studied changes in the cardiac function throughout gestation in fetuses with increased nuchal translucency. They evaluated the *E* and *A* peak velocities of the Doppler waveform of the ventricular filling, the *E*/*A* ratio, outflow velocities, stroke volume, and cardiac output. The authors reported discrepancies in cardiac function parameters between the two cardiac ventricles with a predominant function of the right ventricle. Ninno et al. [97] reported the evaluation of the tricuspid valve during the 11–13 + 6 week scan and showed an increment in the *E* velocity and in the *E*/*A* ratios, and mild changes in the *A* velocity as gestation progresses.

Rozmus-Warcholinska et al. [58] reported normal values for fetal cardiac function parameters between 11 and 13 + 6 weeks of gestation. The authors showed a mild difference in the Tei index (MPI, or myocardial performance index) between the left and right ventricles, and stable values of the Tei index during that period. There was an increment in the *E*/*A* ratio and in the *E* velocity but no changes in the *A* velocity during the same gestational period.

Turan et al. [98] reported a high association between abnormal fetal cardiac function parameters in early pregnancy and maternal hyperglycemia in women with pregestational diabetes. The authors showed reduced left *E*/*A* ratio, prolongation of the isovolumetric relaxation time in both ventricles, reduction in the isovolumetric contraction time in the left ventricle, and prolonged MPI in the two ventricles.

Do We Have to Evaluate All Patients at 11–13 + 6 Weeks?

Gardiner [99] suggested caution in proposing an extended cardiac examination in the first trimester of pregnancy due to the risk of false-positive cases in which parents might decide to terminate the pregnancy in a structurally normal fetus. The author mentioned that, based on morphologic information provided by high-resolution episcopic microscopy (HREM), growth of the atrioventricular septum occurs later in the first trimester of pregnancy, and offset of the mitral and tricuspid valves might not be visualized before 14 weeks of gestation in a structurally normal fetus. The author concluded that there is a high risk of incorrect diagnoses of atrioventricular septal defects in early pregnancy. Volpe et al. [100] evaluated the contribution of the first- and second-trimester echocardiography in the

Table 11.4 Congenital heart defects that can be identified during the early ultrasound fetal cardiac examination at 11–13+6 weeks of gestation

Cardiac defects that can be detected	Transposition of the great arteries; double outlet right ventricle; hypoplastic left heart
Cardiac defects that might be detected	Coarctation of the aorta Tetralogy of Fallot Canal AV or atrioventricular septal defects Truncus arteriosus (Fig. 11.10)
Cardiac defects unlikely to be detected	Ventricular septal defects Ebstein's anomaly Mild aortic and pulmonary stenosis Cardiac tumors Myocardial hypertrophy Fibroelastosis Abnormal pulmonary venous return

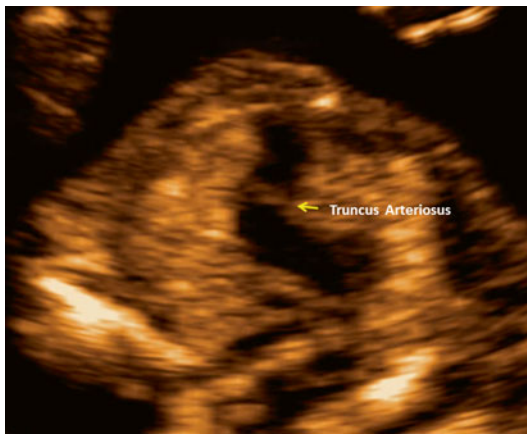

Fig. 11.10 Abnormal outflow tracts: truncus arteriosus

diagnosis of CHD and reported that a considerable proportion of cases, considered as normal in the first trimester examination, might develop cardiac defects at later stages of pregnancy (Table 11.4). Similarly, they reported that a considerable percentage of fetuses with an abnormal cardiac examination might actually have a structurally normal heart.

Safety

Guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG, 2011) recommend keeping the thermal index (TI) < 1.0 during Doppler examination at 11–13+6 weeks. They suggest that the main reason for advocating the principle of ALARA (As Low As Reasonably Achievable) in the first trimester of pregnancy is the unknown effect of Doppler ultrasound during embryogenesis [101]. Nemescu et al. [102] assessed the safety of first trimester fetal echocardiography by measuring the TI and mechanical index (MI) generated during 399 examinations. Although there was an increase in TI values from B mode to color flow to power Doppler studies, these values were always lower than 0.5. Satisfactory Doppler images were obtained with these settings.

Teaching Points

- Early evaluation of the fetal heart as a screening or indicated procedure should be considered based on the availability of technological resources and on the experience of operators.
- Experience and training are the most important factors for early identification of fetal cardiac defects; highly trained operators achieve a better detection rate.
- Increased nuchal translucency, tricuspid regurgitation, reversed A wave in the ductus venosus, aberrant right subclavian artery, abnormal cardiac axis, hydrops, monochorionic twins, pregnancies from assisted reproductive techniques, and any other fetal structural defect are indications for early fetal cardiac ultrasound evaluation.
- Before 12 weeks of gestation transvaginal ultrasound provides adequate images for cardiac examination; from 13 weeks onwards, transabdominal ultrasound also provides reliable cardiac images.
- The 4-chamber and outflow tracts views are the most important ultrasound images to achieve a good detection of congenital heart defects.
- The 4-chamber view and outflow tracts can be identified from 12 weeks of gestation in almost all fetuses. The majority of cardiac planes of the basic and extended fetal cardiac evaluations can be obtained from 13 weeks of pregnancy.

- Additional US techniques such as color directional Doppler and STIC (spatiotemporal image correlation) can contribute in improving the detection rate of congenital heart defects in early pregnancy.

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Doppler Sonography in Early Pregnancy

12

Dev Maulik, Timothy L. Bennett, Blake Porter, Shilpa Babbar, and Devika Maulik

Introduction

Since its introduction to obstetrical practice a few decades ago, Doppler sonography has revolutionized fetal and maternal investigations [1, 2]. Spectral and color Doppler ultrasound provides noninvasively relevant hemodynamic information [3], and its clinical applications have been widespread from high-risk fetal surveillance to fetal echocardiography [4, 5]. It is also useful as an adjunct to fetal ultrasound screening. Although these applications have been mostly limited to the second and third trimesters of pregnancy, Doppler ultrasound of fetal and maternal circulations has also been used during the first trimester. Over the years, various investigators have demonstrated the value and limitations for the first-trimester Doppler sonography for risk assessments in early pregnancy. The most prevalent first-trimester applications include Doppler assessment of the fetal ductus venosus and tricuspid flow, and the maternal uterine artery flow. This chapter reviews these applications, specifically addressing the following:

1. Ductus venosus Doppler during the first trimester and its applications in screening for aneuploidy and congenital heart disease.
2. Tricuspid Doppler flow assessment and its applications in screening for aneuploidy and congenital heart disease.
3. Doppler of the uterine artery in the prediction of subsequent development of preeclampsia.

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Doppler Sonography of the Ductus Venosus

Anatomy and Hemodynamics

The ductus venosus is a venous shunt preferentially streaming oxygenated blood from the placenta, via the umbilical vein, to the fetal heart and brain. Although it has been traditionally depicted as an anatomically contiguous vascular structure with the umbilical vein, more recent autopsy dissections in 14- to 19-week fetuses demonstrated that the umbilical vein ends in the portal sinus, a venous confluence that gives rise to ductus venosus and the right and left portal veins [6] (Fig. 12.1). The ductus venosus is a conical branchless structure with a narrower proximal inlet, called the isthmus, and a wider distal outlet that joins the portal sinus. This configuration increases the velocity of blood flow, propelling it to the foramen ovale and onto the left atrium. Interrelationship between the umbilical vein, ductus venosus and hepatic-portal circulations, in maintaining the perfusion of vital organs, is complex. Under pathological conditions, such as fetal growth restriction, oxygen and nutrient delivery to the heart and brain is maintained by increasing the ductus venosus blood flow, at the cost of perfusion of the liver [7].

Although its presence was recognized since the sixteenth century, the importance of the ductus venosus in fetal circulatory physiology and pathology has been appreciated only very recently, with the advent of Doppler sonography [8]. A detailed discussion of the ductus venosus is beyond the scope of this chapter, but Kiserud has comprehensively reviewed the topic elsewhere [9, 10]. Utilizing two dimensional, color Doppler and pulsed spectral Doppler sonography, Kiserud and colleagues studied longitudinally the ductus venosus flow in normal women from 18 weeks to term, and noted an increase in the mean peak velocity with the progression of gestation. They also reported reversed flow during atrial systole in two cases with fetal cardiac disease. Numerous investigators over the last two decades demonstrated the value of ductus venosus Doppler in understanding circulatory pathophysiology, as well as its prognostic utility in complicated pregnancies, especially with fetal growth restriction [11]. Subsequent studies have reported the potential of ductus venosus Doppler in prenatal risk assessment for aneuploidy and congenital cardiac disease in the first trimester of pregnancy, which is discussed in this review.

Doppler Imaging Technique for the Ductus Venosus

Optimal imaging technique for Doppler interrogation of the ductus venosus has been well described [12, 13]. The ultrasound modalities include two-dimensional, color flow Doppler, and spectral Doppler imaging. The essential guidelines are as follows.

The high-pass filter is set as low as permitted by the device and is usually set at about 50 Hz level. An adequate Doppler frequency range should be selected to accommodate peak velocities without aliasing. The acoustic power output (the mechanical and thermal indices) should be set at a level as low as practically achievable for adequate image quality following the ALARA principle [14]. Anterior sagittal fetal plane is optimal for imaging the ductus (Fig. 12.2). However, posterior sagittal plane may also be helpful. These approaches allow viewing the ductus venosus in a long axis, displaying aliased high velocity color flow at the isthmus and enabling optimal pulsed spectral Doppler interrogation with a minimal insonation angle. In difficult fetal positions, an oblique cross sectional view may be the only choice; however, this will limit imaging at an optimal angle. In early pregnancy, the fetal image should be large enough to include just abdomen and thorax. This minimizes measurement errors related to small size. The sample volume should be adjusted to include only the target vein in order to avoid collecting signals from other veins in proximity, such as the umbilical vein, the hepatic vein or the inferior vena cava. Imaging should be performed only when the fetus is at rest, without body movements, breathing or hiccups.

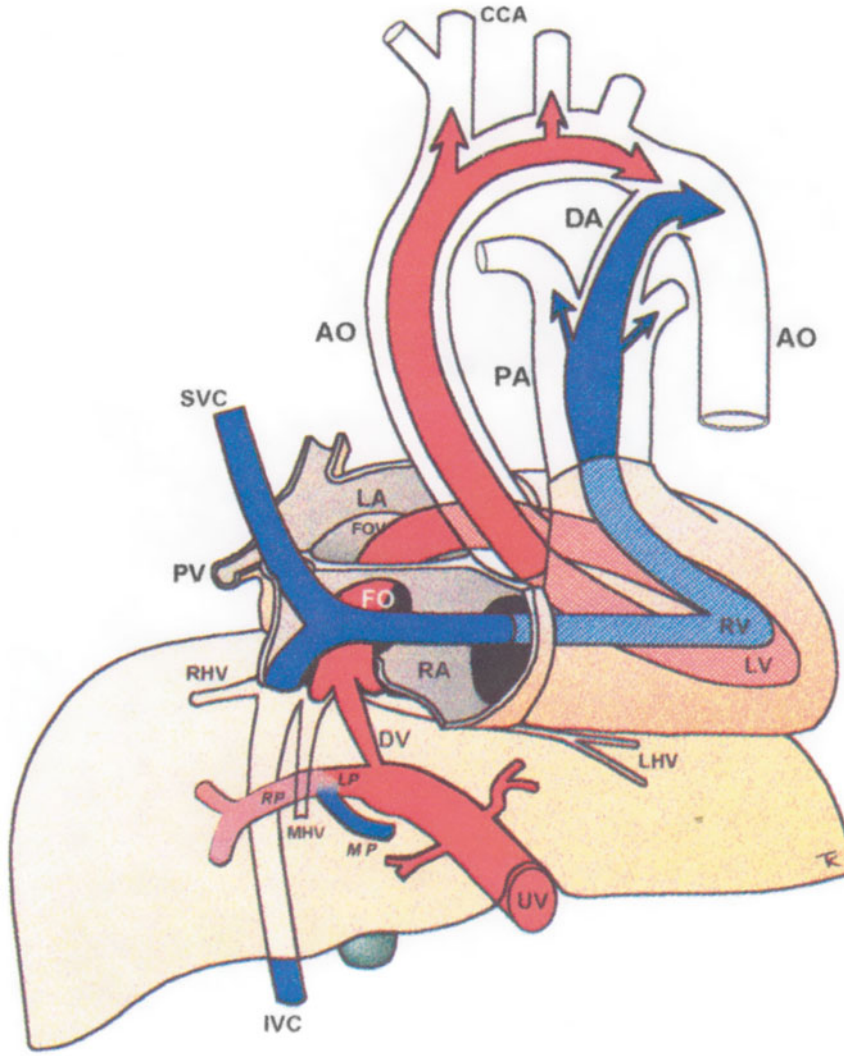

Fig. 12.1 Fetal circulatory pathways showing the three shunts, ductus arteriosus (DA), ductus venosus (DV), and the foramen ovale (FO). The via *sinistra* (*red*) directs blood from the umbilical vein (UV) through the DV and FO to reach the left atrium (LA), left ventricle (LV) and ascending aorta (AO) thus supplying the coronary and cerebral circuit with well oxygenated blood before joining with the via *dextra* (*blue*) in the descending AO. The via dextra receives deoxygenated blood from the abdominal inferior vena cava (IVC) and superior vena cava (SVC) directed to the right atrium (RA), right ventricle (RV), pulmonary trunk (PA) bypassing the pulmonary circuit through the DA. Splanchnic blood from the main portal stem (MP) is provided to the right liver lobe after blending with umbilical blood that reaches the right portal branch (RP) through the left branch (LP). *CCA* common carotid arteries, *FOV* foramen ovale valve, *LHV* left hepatic vein, *MHV* medial hepatic vein, *PV* pulmonary vein. With kind permission from Springer Science+Business Media: Ductus venosus, Kiserud T. In: Doppler ultrasound in obstetrics and gynecology, 2nd ed., Maulik D, Zalud I, editors, 2005

Ductus Venosus Doppler Waveforms

In normal pregnancies, blood flow in the ductus venosus is directed toward the fetal heart. The Doppler waveform is triphasic with two peaks and a trough reflecting the phases of the fetal cardiac cycle (see Fig. 12.2). The first peak is the highest velocity during the ventricular systole and is designated as the S wave. The second peak, termed the D wave, is the highest velocity during

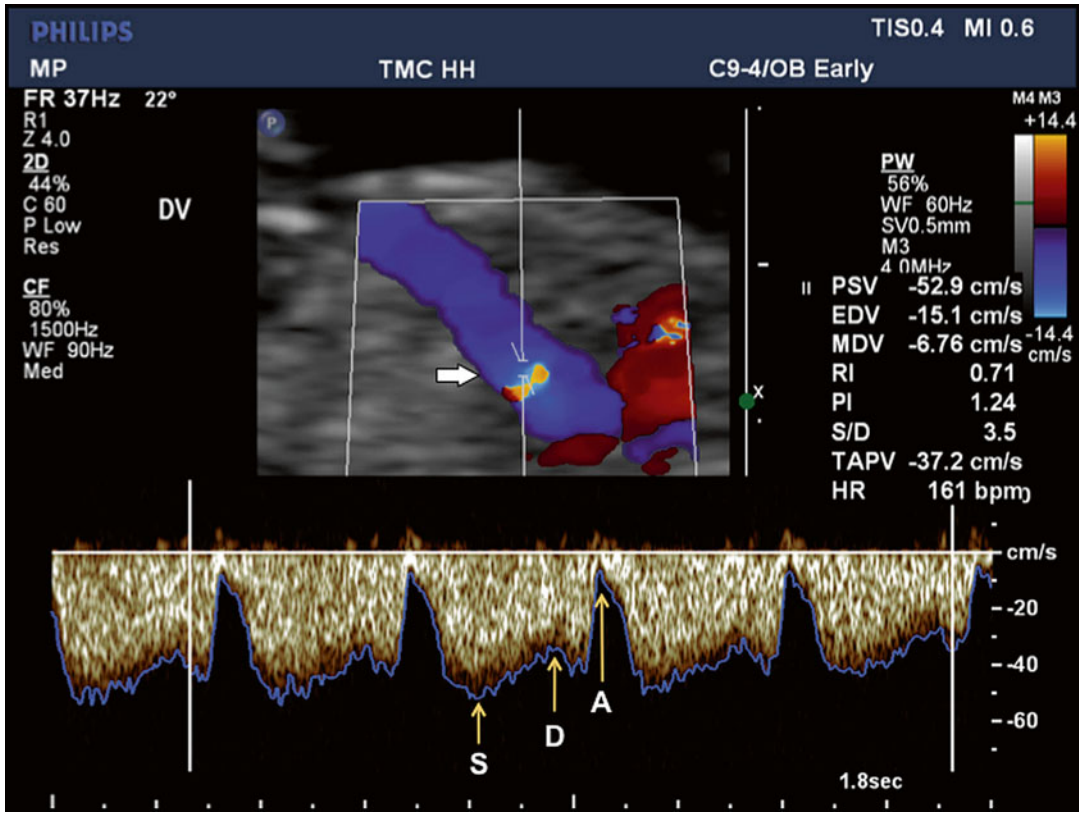

Fig. 12.2 Doppler ultrasound imaging of ductus venosus flow in the sagittal plane at 12 weeks' gestation is depicted in color Doppler and spectral Doppler modes. The *upper panel* shows color Doppler flow pattern with aliasing related to high velocity, which guides the placement of the Doppler sample volume (*horizontal arrow*). The flow is away from the transducer as indicated by the color map. The *lower panel* depicts the triphasic spectral waveforms from the ductus. In this display, the *blue line* corresponds to the peak velocity envelope through the cardiac cycle. S, peak systolic velocity; D, peak diastolic velocity; A, lowest peak velocity due to atrial contraction

the ventricular diastole and is lower than the S wave. The trough, called the a-wave, is the lowest velocity of the Doppler waveform corresponding to the minimum velocity during the atrial contraction. The Doppler waveforms from the ductus venosus can be analyzed in terms of the actual velocity values, which require an optimal insonation angle and angle correction. Alternatively, various indices of pulsatility have been described which obviates the need for angle correction. In all these measurements the maximum frequency shift envelope of the waveform is utilized (see Fig. 12.2).

In clinical practice, the most relevant and frequently used attribute is the a-wave, which is related to the atrial contraction. A zero or negative waveform indicates an increased end-diastolic filling pressure in the right heart (Fig. 12.3).

Factors Affecting the Ductus Venosus Waveform

In early pregnancy, the velocity of blood flow in the ductus venosus increases with gestational age. The increase is throughout the fetal cardiac cycle. In a cross-sectional study of 262 normal singleton fetuses between 8 and 20 weeks gestation, van Splunder and associates noted a significant nonlinear rise in S, D and time-averaged

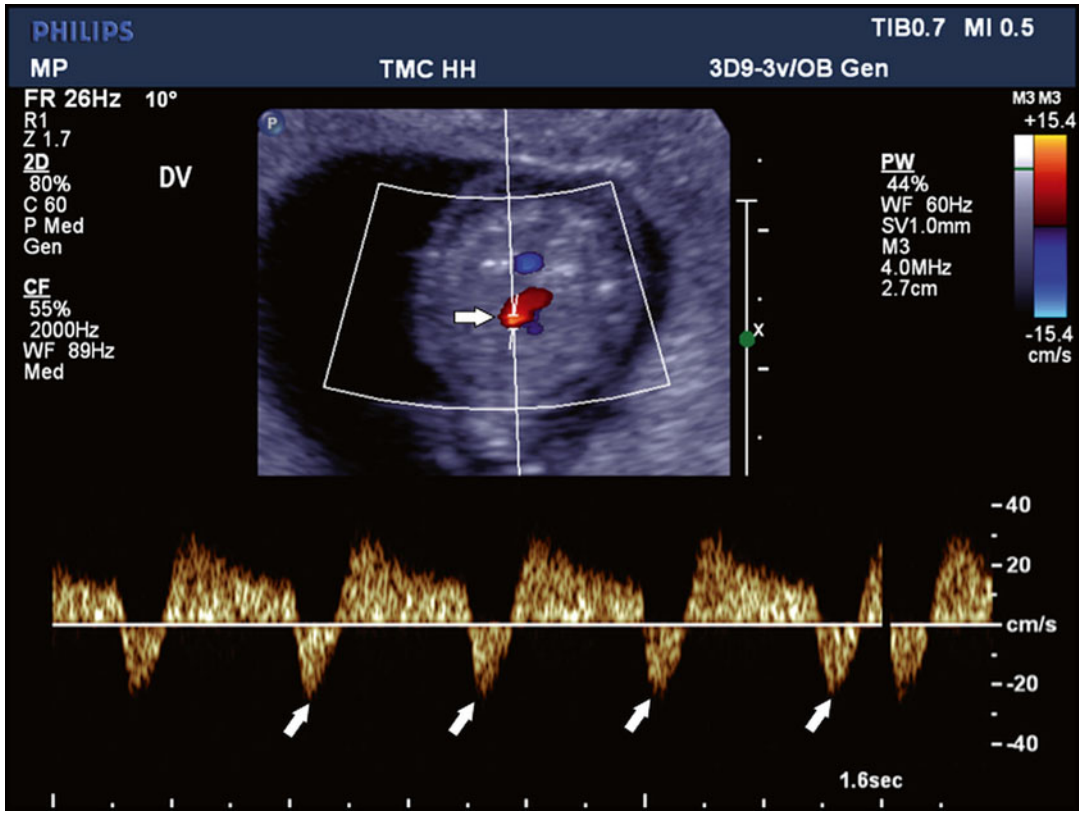

Fig. 12.3 Reversal of flow in the ductus venosus is depicted in color Doppler directed spectral Doppler display. The *upper panel*, in the oblique axial plane, shows the color Doppler flow in the ductus and the *lower panel* the spectral display. The oblique *arrows* indicate reversal of flow. The *horizontal arrow* shows the placement of the Doppler sample volume

peak velocity (Vta) but a significant decline in the pulsatility index for veins (PIV) [15]. The Vta increased almost fourfold. Prefumo and colleagues measured the ductus venosus velocity parameters between 10 and 14 weeks in 201 normal fetuses in a cross-sectional study [16]. During this period, the mean S wave increased from 27 to 33.6 cm/s, the mean a-wave from 5.9 to 7.8 cm/s, and the time-averaged peak velocity from 19.4 to 25.3 cm/s. These increases level off beyond the first half of pregnancy. The reference ranges for the ductus venosus Doppler velocity components from this study are depicted in Figs. 12.4, 12.5, 12.6, and 12.7.

Fetal breathing movements produce intrathoracic pressure fluctuations, leading to changes in the venous pressure dynamics. Breathing induced pressure gradients of up to 22 mmHg across the ductus venosus have been estimated in fetuses during 18–40 weeks of pregnancy utilizing the Bernoulli equation [17]. This is the rationale for not assessing the ductus venosus Doppler hemodynamics during fetal breathing. Breathing movements in early gestation are not regular and become more frequent as the fetus approaches mid-gestation [18]. There is a dearth of information regarding the quantitative effects of breathing movements on precordial venous dynamic in early pregnancy. Fetal movements will also affect the Doppler shift.

Fetal heart rate affects ductus venosus Doppler waveform. Bradycardia allows an increased venous return and atrial filling, leading to an enhanced atrial contraction and, consequently, an enhanced a-wave. In a sheep model, Gudmundsson and coworkers noted changes in

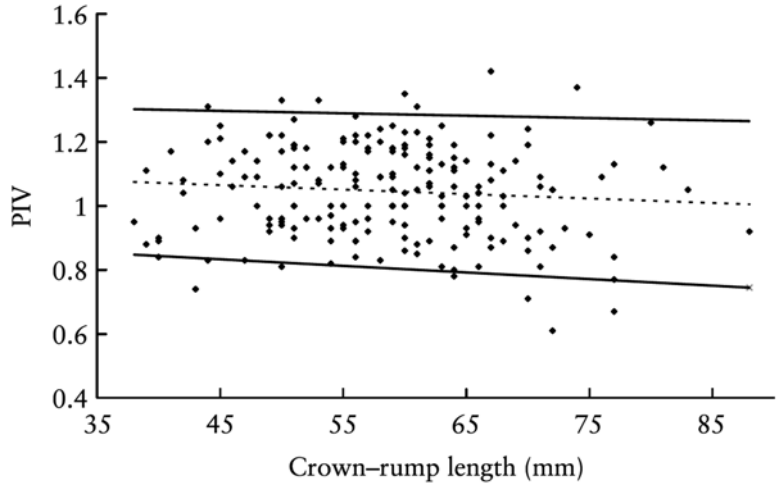

Fig. 12.4 Ductus venosus pulsatility index for veins (PIV) measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. The equation for the 50th centile is $y = -0.0014x + 1.1279$ and for the standard deviation is $SD = 0.0004x + 0.1233$. Reprinted from Prefumo F, Risso D, Venturini PL, De Biasio P. Reference values for ductus venosus Doppler flow measurements at 10–14 weeks of gestation. Ultrasound Obstet Gynecol. 2002;20(1):42–6, with permission from John Wiley & Sons

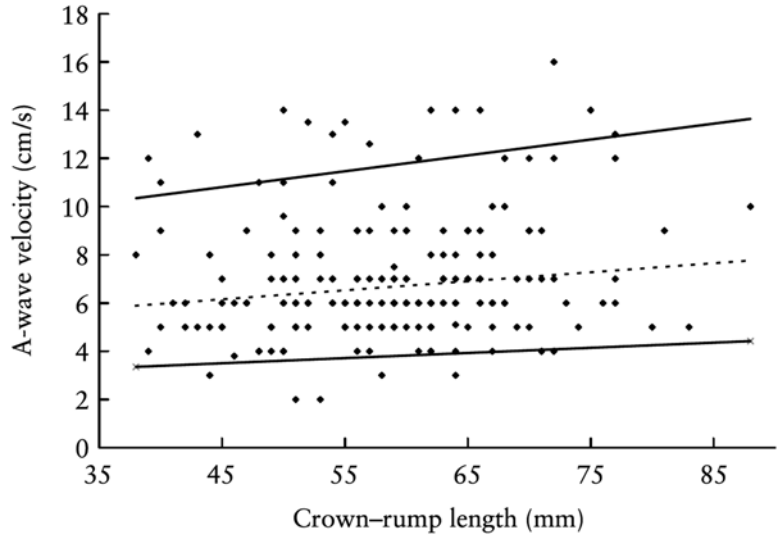

Fig. 12.5 Ductus venosus S-wave velocity measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. The equation for the 50th centile is $y = 0.1304x + 22.083$ and for the standard deviation is $SD = 0.0448x + 4.862$. Reprinted from Prefumo F, Risso D, Venturini PL, De Biasio P. Reference values for ductus venosus Doppler flow measurements at 10–14 weeks of gestation. Ultrasound Obstet Gynecol. 2002;20(1):42–6, with permission from John Wiley & Sons

ductus venosus velocity waveform directly related to fetal bradycardia consequent to fetal hypoxemia, [19]. Any increase in the fetal myocardial compliance will lead to changes in the ductal waveform. Thus, hypoxia, acidosis or intra-thoracic lesions such as pleural effusion pressing on the heart lower cardiac compliance, leading to augmented a-waves [9, 13]. Blood viscosity also modifies venous Doppler waveforms, which is seen in fetal anemia. Lam and co-investigators reported significant increases in S, a-wave and Vta in nonhydropic fetuses between 12 and 13 weeks with homozygous alpha thalassemia-1 [20]. This was attributed to lower blood viscosity in anemia and also to hypoxia.

Ductus Venosus Doppler in First-Trimester Aneuploidy Screen

The most frequent and important utilization of ductus venosus Doppler in the first trimester of pregnancy is for aneuploidy screening. Various investigators have demonstrated its efficacy, with

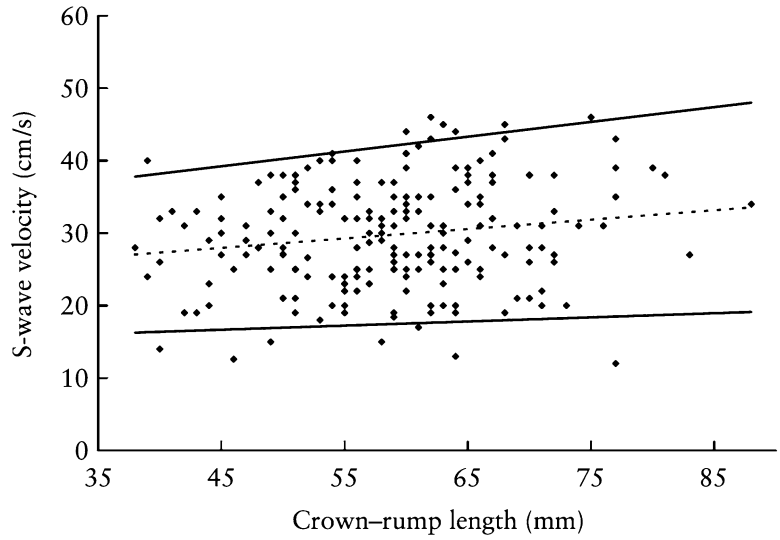

Fig. 12.6 Ductus venosus A-wave velocity measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. Log_{10} transformation was performed for data analysis; data are displayed after antilog transformation. The equation for the 50th centile is $y = 10^{0.0024x+0.679}$ and the standard deviation is $SD = 10^{0.1492}$. Reprinted from Prefumo F, Risso D, Venturini PL, De Biasio P. Reference values for ductus venosus Doppler flow measurements at 10–14 weeks of gestation. Ultrasound Obstet Gynecol. 2002;20(1):42–6, with permission from John Wiley & Sons

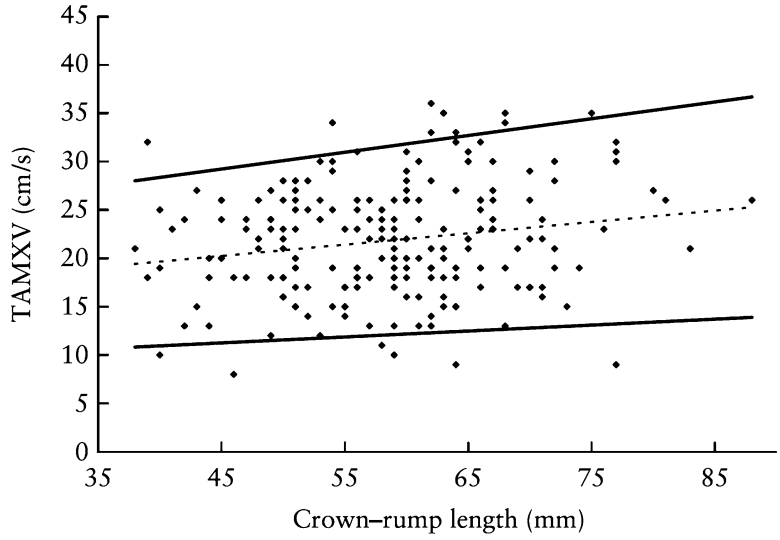

Fig. 12.7 Ductus venosus time-averaged maximum velocity (TAMXV) measurements according to crown-rump length in 198 fetuses presented with 5th, 50th and 95th centiles. The equation for the 50th centile is $y = 0.1174x + 14.95$ and for the standard deviation is $SD = 0.0342x + 3.9375$. Reprinted from Prefumo F, Risso D, Venturini PL, De Biasio P. Reference values for ductus venosus Doppler flow measurements at 10–14 weeks of gestation. Ultrasound Obstet Gynecol. 2002;20(1):42–6, with permission from John Wiley & Sons

or without the nuchal translucency and various biomarkers. Selected reports are discussed below and summarized in Table 12.1 [21–30].

Borrell and colleagues reported Doppler velocimetry of the ductus venosus, prior to performing invasive diagnostic procedures for trisomy 21, in

Table 12.1 Reported abnormal ductus venosus doppler in fetal aneuploidy in the first trimester of pregnancy

First author (reference)	Date	Total patients	Euploid cases	Aneuploid cases	Abnormal DVD aneuploid cases (%)	Abnormal DVD in euploid fetuses (%)
Matias [22]	1998	486	423	63	90.5	3.07
Antolin [23]	2001	924	911	13	77.0	4.28
Murta [24]	2002	372	343	29	89.7	2.04
Zoppi [25]	2002	325	292	33	69.7	13.0
Borrell [26][a]	2003	3382	3289	93	64.5	4.93
Toyama [27]	2004	1097	1075	22	68.2	6.42
Prefumo [28]	2005	572	497	47[b]	[c]	5.23
Maiz [29]	2009	19,800	19,614	186	64.0	3.17
Florjański [30]	2013	1526	1480	46	63.0	7.43
Totals		28,484	27,924	532	69.9	3.89

DVD ductus venosus Doppler
[a]Forty cases were defined as euploid cases due to being either placental mosaicism or a balanced translocation
[b]Only trisomy 21 cases
[c]Data not reported given that not all aneuploid cases in this study had DVD findings reported

534 consecutive fetuses of 10–18 weeks of gestation [21]. Trisomy 21 was present in 11 fetuses, eight of whom had venous pulsatility index >95th centile, and three had the a-wave below 5th centile. Matias and coworkers performed Doppler velocimetry of the ductus venosus, just before fetal karyotyping, in 486 consecutive singleton pregnancies between 10 and 14 weeks [22]. Of the 63 fetuses with chromosomal anomaly, 57 (90.5 %) had reverse or absent a-wave. Abnormal ductus venosus Doppler was also observed, however, in 13 (3.1 %) of the 423 euploid fetuses. Multivariate regression analysis demonstrated that only the abnormal a-wave offered a significant independent discrimination between the euploid and the aneuploid cases.

In a cohort of about 20,000 singleton pregnancies, Maiz and colleagues performed a combined first-trimester screening test, comprising maternal age, fetal nuchal translucency thickness, fetal heart rate, serum free beta-human chorionic gonadotropin, pregnancy-associated plasma protein-A (PAPP-A), and the ductus venosus Doppler [29]. The a-wave was reversed in 66–75 % of aneuploid, but in only 3.2 % of euploid fetuses. Universal inclusion of the first-trimester ductus venosus Doppler would detect 96 %, 92 %, 100 % and 100 % of trisomies 21, 18 and 13 and Turner syndrome, respectively, at a false-positive rate of 3 %. Similar detection rates were achieved in a two-step strategy with a false-positive rate of 2.6 %, necessitating ductus venosus Doppler in only 15 % of the total population.

It should be appreciated that most fetuses with abnormal ductus venosus Doppler are euploid and not all fetus with aneuploidy will have abnormal findings. As shown in Table 12.1, which summarizes several studies on first-trimester ductus venosus Doppler, abnormal Doppler findings were present in 70 % of aneuploid fetuses, but only in 4 % of the euploid fetuses (see Table 12.1).

Obviously, prenatal noninvasive risk assessment for chromosomal abnormalities during early gestation involves multiple modalities, such as the sonographic assessment of nuchal translucency and measurement of multiple analytes. The efficacy of incorporating the ductus venosus Doppler in these algorithms is further discussed later.

Ductus Venosus Doppler Screening for Congenital Heart Disease

Ductus venosus Doppler waveforms reflect fetal central hemodynamics, especially that of the right heart. Functional and anatomical abnormalities are expected to alter this waveform. This prompted many to explore its screening potential for the early detection of fetal cardiac disease.

Matias and coworkers performed Doppler velocimetry of the ductus venosus in 200 singleton fetuses with increased nuchal translucency, at 10–14 weeks' gestation, immediately before fetal karyotyping [22]. The results suggested that in euploid fetuses with increased nuchal translucency, the presence of abnormal ductus venosus blood flow recognized those with major cardiac defects.

In a study involving over 41,000 euploid fetuses, reversal of ductus venosus a-wave was observed in about 28 % of the fetuses with cardiac anomalies and in about 2 % of the fetuses with no cardiac anomalies [31]. The authors estimated that comprehensive fetal echocardiography would detect approximately 39 % of major cardiac defects, at an overall false-positive rate of about 3 %, in cases with nuchal translucency above the 99th centile and those with reversed a-wave, independent of the nuchal translucency measurement.

This has been further confirmed, more recently, by Borrell and associates who studied the efficacy of various first-trimester ultrasound screening strategies for the recognition of major cardiac malformations, in euploid fetuses [32]. The sonographic methods included fetal nuchal translucency and Doppler indices of the ductus venosus. If the ultrasound findings were abnormal, early echocardiography was recommended. Verification of the fetal cardiac status was performed by fetal echocardiography in mid- and late gestation, neonatal assessment or autopsy. Of the 37 euploid fetuses with a major cardiac malformation, the nuchal translucency was above the 99th centile in 27 % cases and the ductus venosus a-wave was absent or reversed in 39 % of the fetuses. The authors noted a 47 % detection rate of major heart defects, with a false positive rate of about 3 %.

These and other investigations suggest a role for ductus venosus Doppler to identify early those fetuses at a higher risk of CHD. Early fetal echocardiography can be challenging and may not obviate the need for comprehensive ultrasound examination at mid-pregnancy. However, Zidere and associates recently demonstrated that, in expert hands, it could achieve a high degree of accuracy [33]. Future research should further address the effectiveness of early fetal echocardiography in clinical practice.

Doppler Investigation of Tricuspid Flow in the First Trimester

Over the recent years, there has been a progressively wider use of Doppler echocardiography for assessing fetal cardiac function in early pregnancy. Of the various aspects of fetal cardiac function, the tricuspid flow patterns have received the most attention, especially regarding its association with congenital cardiac malformations and aneuploidy.

Doppler Insonation Technique

The Doppler echocardiographic modalities used for assessing tricuspid flow include two-dimensional image of the fetal heart, which directs spectral Doppler interrogation. It is beyond the scope of this review to discuss the technique in detail. The principles are essentially the same as in later gestation [5]; however, Huggon and associates have addressed the specific technical issues related to first-trimester application [34]. Briefly, an apical or a basal four chamber view is preferred, as it allows aligning the Doppler beam with the atrioventricular flow direction, with a minimal angle of insonation, which should be kept below 30°. As described earlier with the ductus venosus Doppler, the high pass filter should be set to the lowest level allowed by the device, and the power output should be kept as low as possible. Color Doppler flow will show reversed flow related to the regurgitation and color M-mode has the advantage of providing more accurate temporal resolution. However, color modes are seldom used for the first-trimester screening, because of their inconsistency in depicting intracardiac flow in early gestation. In common practice, spectral Doppler interrogation is guided by two-dimensional B mode imaging, which assists in placing the Doppler sample volume across the tricuspid valves.

Tricuspid Flow Pattern

Spectral Doppler insonation of the atrioventricular flow reveals a biphasic flow pattern, reflecting the contributions of ventricular relaxation and atrial contractions to the Doppler flow velocity waveforms (Fig. 12.8). The first peak, called the E wave, represents the peak flow velocity due to the atrial systole. The second peak, A wave, is the peak flow velocity caused by the ventricular diastole. In the right heart, the A wave is substantially greater than the E wave, whereas in the left heart the waves are less discrepant. This observation suggests a physiologically lower compliance of the right ventricle compared to the left. Neonates and infants demonstrate a similar pattern.

Tricuspid Regurgitation

Normal atrioventricular flow is unidirectional, from the atrium to the ventricle. Reversal of this pattern indicates tricuspid incompetence, with the flow regurgitating from the right ventricle to the right atrium (Fig. 12.9). In the fetus, however, this finding is not always pathological. Utilizing color Doppler, Maulik et al. noted mild tricuspid regurgitation in normal fetuses in mid-pregnancy [35]. Others have extensively demonstrated this.

For example, utilizing color Doppler and color M-mode, Gembruch et al. demonstrated a 6 % prevalence of tricuspid regurgitation in a cross-sectional study of 289 normal singleton fetuses [36]. Makikallio and associates utilized Doppler

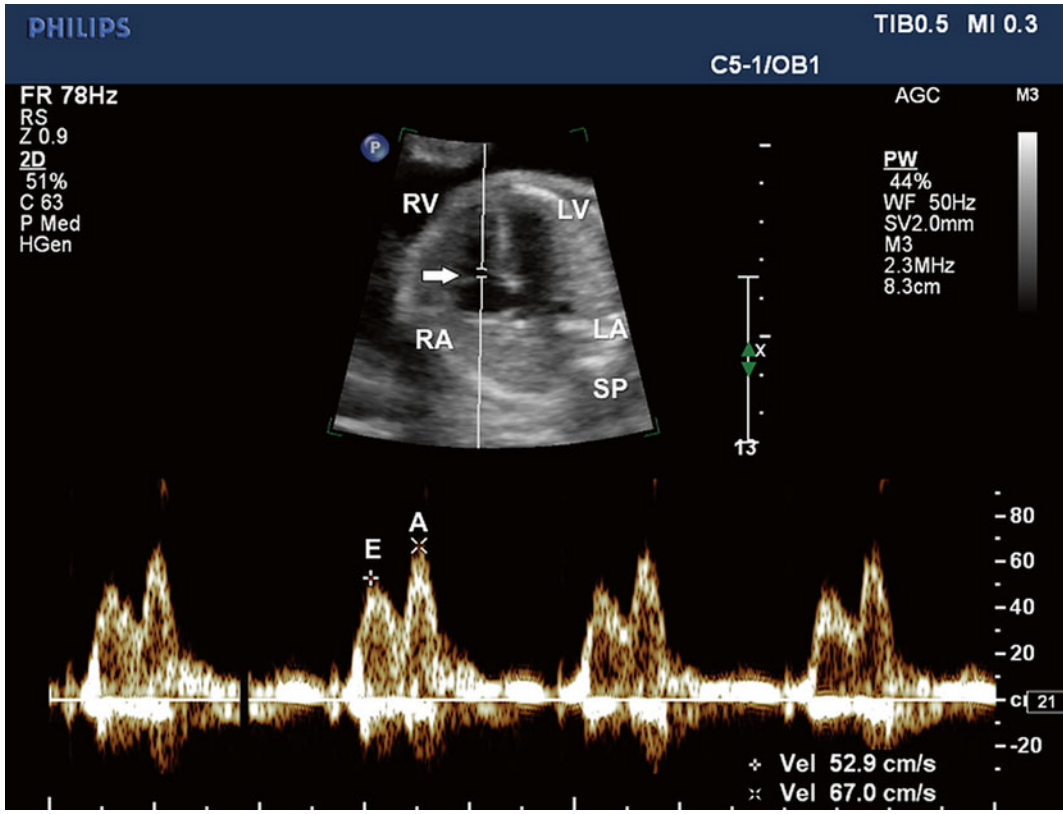

Fig. 12.8 Doppler imaging of the tricuspid flow in the first trimester of pregnancy is depicted here. The *upper panel* shows two-dimensional echocardiography of an apical four-chamber view of the fetal heart at 13 weeks' gestation. The *horizontal arrow* indicates the Doppler sampling location. Note the optimal alignment of the ultrasound beam path with the flow direction (*vertical white line*). The Doppler spectral display of the biphasic blood flow velocities across the tricuspid orifice is shown in the *lower panel*. E, peak flow velocity during ventricular diastole; A, peak flow velocity during the atrial systole; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; SP, spine

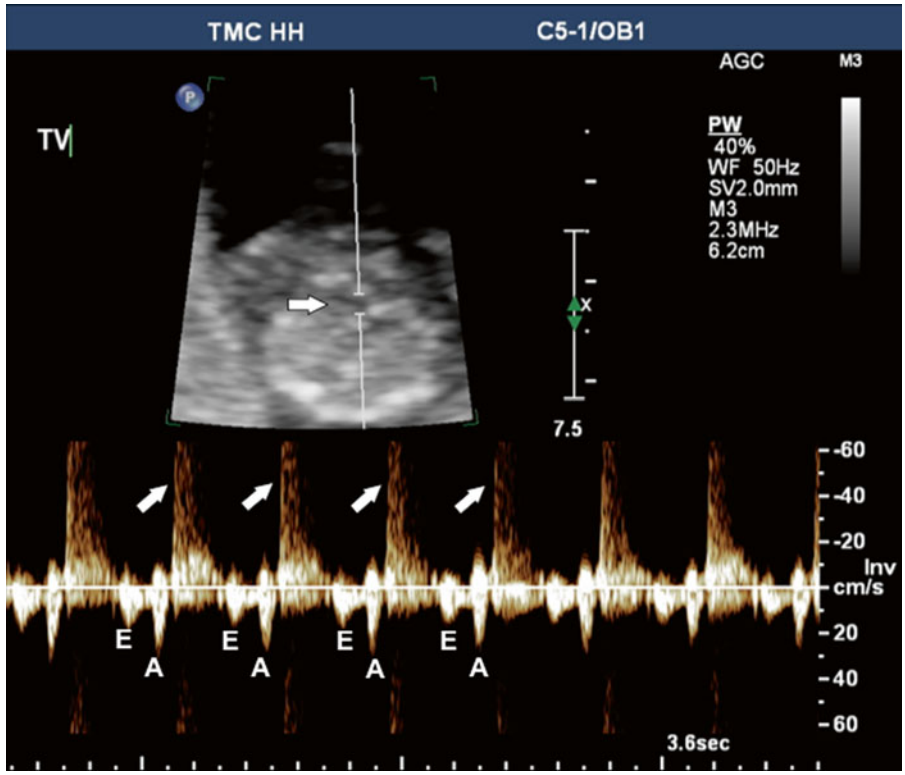

Fig. 12.9 The sonogram illustrates tricuspid regurgitation in a first trimester fetus. The *upper panel* shows placement of the Doppler sample volume. E, peak flow velocity during ventricular diastole; A, peak flow velocity during the atrial systole. The upward oblique *arrows* indicate the high velocity regurgitant flow jets from the right ventricle to the right atrium. Note aliasing of the flow jets due to their high velocity

echocardiography to characterize fetal cardiac function in 16 uncomplicated pregnancies, between 6 and 10 weeks [37]. They noted that the atrioventricular flow was initially monophasic and became biphasic after 9+ weeks. The regurgitant atrioventricular flow was common after 10 weeks. The isovolumetric relaxation time significantly increased from 6 to 7 weeks, indicating progressive maturation of fetal cardiac diastolic function.

Tricuspid Doppler Screening for Aneuploidy and Congenital Heart Disease

Rizzo and colleagues performed Doppler echocardiography to investigate cardiac function in 20- to 23-week euploid fetuses with an elevated nuchal translucency, but without any major malformations, and observed that the ratios between the E-wave and A-wave and the ratios between the E-wave and time velocity integral were significantly decreased at both the mitral and tricuspid valves, suggesting diastolic dysfunction [38]. Lopes and colleagues performed echocardiography in 275 fetuses with elevated nuchal translucency between 12 and 16 weeks' gestation [39]. Subsequent follow up included fetal and neonatal echocardiography, chromosomal analyses, and autopsy. Structural malformations were detected in 37 (14 %) and functional abnormalities in 24 (9 %) fetuses. Of the latter group, 2 (8.3 %) had isolated tricuspid regurgitation and trisomy 21.

Falcon and coworkers comprehensively addressed the role of tricuspid regurgitation in prenatal diagnosis, in 1557 fetuses at 11+0–13+6 weeks' gestation [40]. The authors

successfully performed Doppler assessment of tricuspid flow in 98.8 % cases and observed tricuspid regurgitation in 4.4 % of the euploid fetuses. In contrast, fetuses with trisomy 21 and 18 had a substantially higher occurrence of the regurgitation (67.5 %, 33.3 %, respectively). Moreover, trained sonographers were able to assess reliably tricuspid regurgitation during the first trimester.

Biophysical, Biochemical, and Molecular Screening in Early Pregnancy

With the availability of multiple first-trimester screening tests, including the fetal Doppler and the rapid adoption of cell-free DNA testing, it is immensely important to determine the most effective approach for first-trimester aneuploidy screening. The advent of blood molecular tests may potentially replace personnel-intensive procedures such as nuchal translucency and fetal Doppler measurements. Only a few studies have comprehensively assessed which approach provides the optimal, yet cost-effective, care.

Nicolaides analyzed prospectively collected data to determine the effectiveness of a contingent screening approach for trisomy 21, that combined maternal age, first-trimester biomarkers, and cell-free DNA testing in 93,545 singleton pregnancies [41]. The authors observed that a detection rate of 98 % of fetuses with trisomy 21, with an overall chorionic villous sampling rate <0.5 %, may be accomplished by offering cell-free DNA testing to about 36 %, 21 %, and 11 % of cases identified by first-line screening, using the combined test alone, the combined test with the addition of serum placental growth factor (PlGF) and alpha fetoprotein (AFP), and the combined test with the addition of PIGF, AFP, and ductus venosus Doppler pulsatility index for veins, respectively.

Although cost effective strategies were not specifically analyzed, the authors observed that the existing protocols that include biomarkers, biophysical modalities including venous Doppler, and the use of cell-free DNA in selected cases, would reduce the need for chorionic villous sampling, with a very high detection rate and a very low false positive rate. Although universal cell-free DNA testing would have an even higher detection rate, the cost may substantially increase. Clearly, there are other complex factors that influence the efficacy and economy of the various screening approaches, which requires more focused scrutiny.

Doppler Ultrasound Imaging of the Uterine Artery in the First Trimester

Introduction of Doppler sonography of the uterine artery, a few decades ago, ushered in exciting opportunities to investigate uteroplacental circulation [42]. Its potential was apparent, as this circulation constitutes the maternal supply line to the fetus that is essential for its survival, sustenance and growth. In order to fulfill fetal demand, the uteroplacental circulation undergoes enormous changes that include early transformation of the spiral endometrial arteries, supplying the placental intervillous space, into large conduits of low impedance flow. This is achieved by the invasion of specialized trophoblastic cells that invade and replace the intima and media of these arteries [43]. This process starts in early pregnancy and extends to the myometrial course of these arteries by the middle of second trimester. These changes are reflected in the uterine artery Doppler waveforms. Inadequacy of this remodeling process has been associated with the subsequent development of preeclampsia and fetal growth restriction [44, 45]. This offers a potential for using uterine artery Doppler for the prediction and prognostication of these pregnancy complications. Early investigators used continuous wave Doppler probes but this blind approach was soon replaced by pulsed Doppler interrogation guided by color Doppler imaging [46–48].

Doppler Imaging Technique for the Uterine Artery

Several investigators have described the current methods for Doppler interrogation of the uterine artery and international guidelines exist [13, 49].

In the first trimester, the uterine arteries can be interrogated either transabdominally or transvaginally. In the transabdominal approach, the paracervical site at the level of the internal os is preferred over iliac crossover site as it is easier to obtain. In a prospective longitudinal study of fetuses at 11–13 and 21–22 weeks of gestation, Lefebvre and colleagues successfully obtained adequate Doppler signals from both the uterine arteries in all the cases at the paracervical site at the os level, but only in about 60 % of the cases at the iliac crossover site [50]. Using color Doppler, the uterus and the cervix are imaged in a mid-sagittal plane at the level of the internal os, lateral manipulation of the transducer reveals the ascending branch of the uterine artery, which is sampled to obtain the uterine artery spectral Doppler signals.

In the transvaginal approach, the transducer is placed in the anterior fornix and manipulated laterally. The color Doppler image reveals the uterine artery and pulsed Doppler interrogation is performed. Consistent with the general principles of the Doppler insonation, the angle of insonation should be less than 30°, the frequency range should accommodate the peak velocities without aliasing, the high pass filter should be set at the lowest possible level and the power setting should be minimized consistent with an adequate image quality.

Uterine Artery Doppler Waveform

The uterine artery Doppler waveform in early pregnancy demonstrates a rapid acceleration and deceleration of the flow velocity during systole, followed by an early diastolic deceleration, known as the diastolic notch, and then a slight rise in the late diastole (Fig. 12.10). Factors that

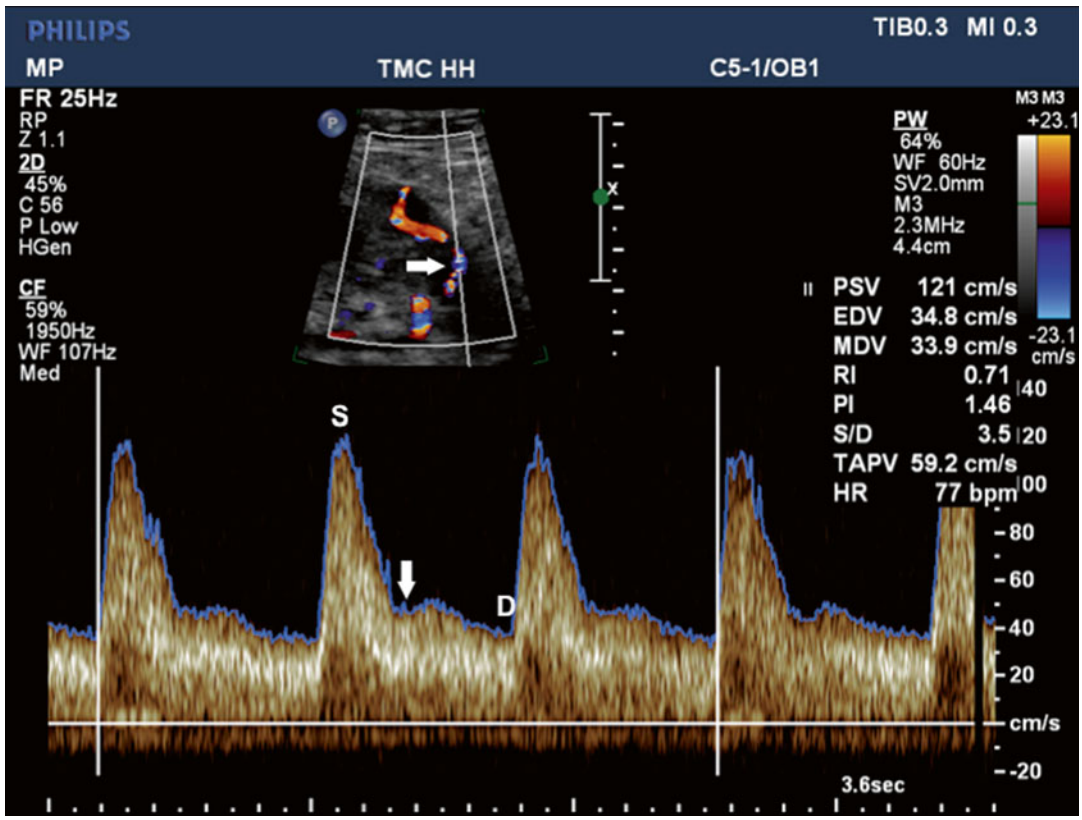

Fig. 12.10 The figure shows uterine artery Doppler waveforms in the first trimester of pregnancy. The *upper panel* shows color Doppler flow in the ascending branch of the uterine artery. The *horizontal arrow* indicates the site of Doppler sampling, The *lower panel* depicts the spectral Doppler waveforms. The *blue margin* of the waveform shows the peak velocity envelope through the maternal cardiac cycle. S, the peak systolic velocity; D, the end diastolic velocity. The *vertical down arrow* indicates the diastolic notch

influence the waveform include gestational age, maternal heart rate, placental location and the location of the measurement in the uterine artery system.

The pulsatility of the waveform declines rapidly between 14 and 16 weeks of pregnancy, then slowly until about 26 weeks, stabilizing thereafter until the end of pregnancy [42]. A more recent study, however, reported a continuous decline until 34 weeks [51]. These changes reflect profound decline in the uteroplacental circulatory impedance during early pregnancy, consequent to the dramatic transformation of the spiral endometrial arteries, with the invasion of the specialized trophoblastic cells.

The effect of maternal heart rate on the diastolic run-off time modifies the waveform and its pulsatility. A higher rate will shorten the diastolic run-off time, leading to a decrease in the pulsatility and vice versa. Uterine artery waveforms from the ipsilateral placental site show a lower pulsatility than those from the contralateral location [52]. Finally, the pulsatility declines as the Doppler sampling site is moved from upstream to downstream, in the uteroplacental arterial system [46]. Thus, Doppler waveforms from the spiral arteries show significantly lower pulsatility than those from the main artery, reflecting progressive decline in the circulatory impedance down the arterial tree.

The pulsatility of the uterine artery waveforms are analyzed utilizing the maximum frequency shift envelope of the Doppler frequency shift (see Fig. 12.10). The standard indices are calculated, including the pulsatility index, resistance index and systolic-diastolic ratio. A high Doppler index is associated with adverse pregnancy outcome, especially development of preeclampsia and/or fetal growth restriction. This is further discussed later. Any transient decelerations, called notches, have been described during the systolic or the diastolic phase [53–55]. Such a notch implies a high impedance in the uterine circulation. Gomez and coworkers noted that bilateral notch declined from about 49 % of the waveforms at 11 weeks to about 14 % at 22 weeks; however its persistence beyond mid-gestation was associated with adverse outcome.

Clinical Applications of the Uterine Artery Doppler

High pulsatility indices and persistent notch in the uterine artery Doppler have been associated with subsequent preeclampsia, fetal growth restriction, and adverse perinatal outcomes [48, 49]. Recent reports have been variably consistent.

In a study involving 3324 consecutive singleton pregnancies, Martin and associates studied the efficacy of uterine artery Doppler, between 11 and 14 weeks of gestation, for the prediction of subsequent development of preeclampsia and fetal growth restriction [56]. Preeclampsia developed in about 2 % and fetal growth restriction in about 10 % of the cases. The sensitivity of a mean pulsatility index > 2.35 was only 12 % for isolated fetal growth restriction and 27.0 % for preeclampsia with or without coexisting fetal growth restriction. However, the sensitivity for these complications requiring delivery before 32 weeks of gestation was 60 % for preeclampsia, and 28 % for fetal growth restriction. Gomez and associates reported that persistence of abnormal Doppler findings, such as bilateral notch and elevated pulsatility index into the second trimester, increased adverse outcomes [51]. The highest risk was related to the persistent abnormal pulsatility index (OR, 10.7; 95 % CI, 3.7–30.9). In a prospective study, however, involving a Scandinavian population, with a prior risk for developing hypertension in pregnancy, Skrastad and colleagues observed only modest efficacy of a first-trimester protocol that combined maternal attributes, mean arterial pressure, uterine artery pulsatility index, PAPP-A, and PIGF [57].

In a systematic review of 74 studies of preeclampsia, with a total population of almost 80,000 patients, Cnossen and associates noted that an elevated uterine pulsatility index with notching carried a positive likelihood ratio of 21 in high-risk and 7.5 in low-risk mothers for developing preeclampsia [58]. For fetal growth restriction, a review of 61 studies, with a population of over 41,000 low risk women, showed a positive likelihood ratio of 14.6 for developing severe growth restriction. Uterine artery Doppler

was more predictive when performed in the second rather than in the first trimester.

Others, however, could not corroborate the predictive efficacy of the first-trimester uterine artery Doppler. Audibert and associated did not observe any further improvement in the predictive efficacy, when the uterine artery Doppler results were combined with biomarkers for the development of preeclampsia [59]. In a prospective cohort study of patients presenting for first-trimester aneuploidy screening between 11 and 14 weeks' gestation, Goetzinger and others observed that, for a fixed false-positive rate of 10 %, A-disintegrin and metalloprotease 12, PAPP-A, and uterine artery Doppler pulsatility index, in combination with maternal attributes, identified 50 %, 48 %, and 52 % of patients who subsequently developed preeclampsia, respectively, and their combination did not enhanced predictive efficiency [60].

There are numerous studies that have addressed the efficacy of early pregnancy uterine artery Doppler for predicting pregnancy complications. In a meta-analysis, involving 18 studies and 55,974 women, Velauthar and associates investigated the efficacy of abnormal uterine artery Doppler for predicting preeclampsia and fetal growth restriction [61]. For the early onset preeclampsia, the sensitivity and specificity were 47.8 % (95 % confidence interval: 39.0–56.8) and 92.1 % (95 % CI: 88.6–94.6), and for early-onset fetal growth restriction they were 39.2 % (95 % CI: 26.3–53.8) and 93.1 % (95 % CI: 90.6–95.0), respectively. For any preeclampsia and fetal growth restriction, the sensitivities were 26.4 % (95 % CI: 22.5–30.8) and 15.4 % (95 % CI:12.4–18.9), respectively, and the specificities were 93.4 % (95 % CI: 90.4–95.5 %) and 93.3 % (95 % CI: 90.9–95.1), respectively. The numbers of women with abnormal Doppler needed to treat with aspirin to prevent one case of early-onset preeclampsia were 173 and 421 for background risks varying between 1 % and 0.4 %, respectively. The authors recommended the use of aspirin in low-risk pregnancies with abnormal uterine artery Dopplers for preventing certain pregnancy complications.

Any such recommendation, however, must be based on the evidence of effectiveness of early pregnancy aspirin prophylaxis. There have been several randomized clinical trials addressing this issue. Yet, none of the studies, had sufficient power. In a meta-analysis of 42 randomized controlled trials of the effectiveness of low-dose aspirin prophylaxis involving 27,222 women, Roberge and associates noted a significant reduction in adverse perinatal outcome, when the prophylactic therapy was initiated at or before 16 weeks of gestation [62]. The selection criteria for therapy included clinical risk factors such as nulliparity and chromic hypertension, as well as abnormal uterine artery Doppler. Initiation of aspirin at or before 16 weeks gestation, as opposed to after 16 weeks, was associated with a 53 % decrease in preeclampsia and an 82 % decrease in severe preeclampsia. Moreover, statistically significant declines in perinatal mortality, fetal growth restriction and preterm births were also observed. This study provides the evidence-based justification for the initiation of low-dose aspirin before 16 weeks in women at risk for preeclampsia or other related adverse outcomes.

Of note, there were no differences in the outcomes, regardless of whether the patients were selected on the basis of risk assessment or abnormal uterine artery Doppler. Obviously, this intriguing finding does not fully establish the role of Doppler assessment, if indeed this simpler, less technology-intensive and low cost approach of risk evaluation is as effective as Doppler. This suggests the need for further investigations with adequate sample size and appropriate study design. The most recent Cochrane review on the uteroplacental Doppler came to a similar conclusion and suggested more research [63].

In summary, uterine artery Doppler in the first trimester of pregnancy has modest to moderate efficacy in identifying women destined to develop preeclampsia. It may also predict other adverse outcomes, including stillbirth, fetal growth restriction and preterm labor. There is evidence of its effectiveness in improving the pregnancy outcome, if low dose aspirin prophylaxis is used before 16 completed weeks of gestation. The intervention is less effective if aspirin is used after 16 weeks' gestation. It is uncertain, however,

whether the addition of the uterine artery Doppler to clinical risk assessment improves the latter's predictive efficacy for implementing early aspirin prophylaxis.

Teaching Points

- First-trimester Doppler of fetal and uterine circulation improves the risk assessment for fetal aneuploidy, congenital heart defects, and subsequent development of preeclampsia.
- Effective use of Doppler sonography in early pregnancy requires appropriate technical training and adhering to the best available evidence.
- First-trimester Doppler of the ductus venosus identifies fetuses at a higher risk of aneuploidy and congenital heart defects.
- The most relevant and frequently utilized attribute of the ductus venosus Doppler is absence or reversal of a-wave.
- Abnormal ductus venosus Doppler is encountered in approximately 70 % of the aneuploid fetuses but only in approximately 4 % of the euploid fetuses.
- The ductus venosus a-wave is absent or reversed in approximately 40 % of the fetuses with major cardiac defects
- First-trimester Doppler assessment of the tricuspid flow enhances the predictive accuracy of early pregnancy aneuploidy screening.
- The presence of tricuspid regurgitation in early pregnancy identifies fetuses at a higher risk of congenital heart defects. It is seen in 67 % of trisomy 21 fetuses but only in 4 % of euploid fetuses.
- The addition of first-trimester fetal ultrasound screening to the biomarkers and selective use of cell-free DNA testing may substantially improve the aneuploidy detection rate and may reduce the need for chorionic villous sampling.
- First-trimester uterine artery Doppler identifies pregnancies at a higher risk of developing preeclampsia and other adverse outcomes.
- Maternal prophylaxis with low-dose aspirin before 16 weeks of gestation reduces subsequent development of preeclampsia.
- It is uncertain whether the addition of the uterine artery Doppler to clinical risk assessment improves the predictive accuracy for implementing early aspirin prophylaxis.

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Three-Dimensional Ultrasound: A Role in Early Pregnancy?

13

Luís F. Gonçalves

Introduction

Although the second-trimester "18- to 22-week" scan is the standard of care for fetal anatomical evaluation, technological progress in ultrasound equipment and high-frequency transvaginal transducers made detailed assessment of the first-trimester fetus a reality [1–9]. High-quality first-trimester ultrasonography represents the first opportunity to identify congenital structural anomalies, usually those at the most severe end of the spectrum [8, 10–13]. Parents whose fetus is diagnosed with major and/or lethal anomalies have the benefit of earlier complementary diagnostic workup and counseling and, if pregnancy termination is a consideration, it can performed earlier and safer than if the same diagnosis was made during the second trimester [11].

This chapter reviews the role of three-dimensional ultrasound (3DUS) as an adjunctive imaging modality to two-dimensional ultrasound (2DUS) for first-trimester diagnosis of congenital anomalies. The reader is reminded that knowledge of embryology, natural history of congenital anomalies, as well as operator experience are likely to have a greater impact on the quality of the first-trimester exam than the availability of high-resolution ultrasound systems equipped with state of the art 3D technology.

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Instrumentation

3DUS can be performed using mechanical or matrix array transducers. First-trimester prenatal diagnosis of congenital anomalies is ideally performed using high-frequency transvaginal probes. If evaluation of the fetal heart is desired, color Doppler is strongly advised, as its use is associated with increased detection rates for congenital heart disease in the first trimester [11, 14–16]. For the examination of the first-trimester heart, volumes are acquired using 4D spatiotemporal image correlation (STIC) technology so that cardiac motion can be analyzed as well [17–20].

Ideal Gestational Age to Perform the Exam

Recent studies indicate that extending the NT examination to include a detailed survey for fetal anomalies, in addition to early fetal echocardiography if the NT is increased, results in a high detection rate for congenital anomalies [11, 12, 16, 21]. Visualization rates for fetal cardiac

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structures is higher after 12 weeks compared to 11 weeks, and even better after 13 weeks, when the aortic root can be more consistently demonstrated [22]. The tradeoff is the upper crown-rump length limit of 84 mm to measure the NT [9]. Therefore, careful scheduling of the examination is advised so that both exams can be performed in a single visit.

Please also note that a high detection rate for fetal anomalies, including congenital heart disease, has been reported with the use of transvaginal ultrasonography by expert sonologists performing such exams between 14 and 17 weeks of gestation [13, 23].

What Can Be Confidently Imaged?

Much of what can be confidently imaged in the first trimester comes from work performed with 2DUS. Table 13.1 provides a list of anatomical structures that may be assessed during the 11–13 6/7 weeks scan [9]. The reader is encouraged to attempt to image structures marked as optional as well, and to push his/her limits beyond the guidelines. For example, with good technique and adequate equipment, the outflow tracts of the fetal heart can be imaged early, and early diagnosis of conotruncal anomalies is possible [5, 14, 24, 25].

Table 13.1 Suggested anatomical assessment at 11 to 13+6 weeks (ISUOG—International Society of Ultrasound in Obstetrics and Gynecology – guidelines)[a]

Organ/ anatomical area	Present and/or normal?
Head	Present
	Cranial bones
	Midline falx
	Choroid-plexus-filled ventricles
Neck	Normal appearance
	Nuchal translucency thickness (if accepted after informed consent and trained/certified operator available)[b]
Face	Eyes with lens[b]
	Nasal bone[b]
	Normal profile/mandible[b]
	Intact lips[b]
Spine	Vertebrae (longitudinal and axial)[b]
	Intact overlying skin[b]
Chest	Symmetrical lung fields
	No effusions or masses
Heart	Cardiac regular activity
	Four symmetrical chambers[b]
Abdomen	Stomach present in left upper quadrant
	Bladder[b]
	Kidneys[b]
Abdominal wall	Normal cord insertion
	No umbilical defects
Extremities	Four limbs each with three segments
	Hands and feet with normal orientation[b]
Placenta	Size and texture
Cord	Three-vessel cord[b]

[a]Adapted with permission from ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2013;41:102–113
[b]Optional structures

Prenatal Diagnosis of Congenital Anomalies by First-Trimester Ultrasound

Since the first reports demonstrating the feasibility of first trimester diagnosis of congenital anomalies in the late 1980s [1, 26, 27], mounting evidence indicates that accurate prenatal diagnosis of several of the more severe anomalies can be accomplished in the first trimester using high-resolution transvaginal ultrasonography [1, 2, 8, 23, 28]. Table 13.2 provides a summary of the studies published until 2014. These studies also provide evidence that, although early and accurate diagnosis of congenital anomalies is possible and allows early decision making, several anomalies may be missed if a second-trimester (or even a third trimester) scan is not performed. Examples of anomalies that can be missed by a first-trimester scan include vermian hypoplasia, agenesis of the corpus callosum, abnormalities of neuronal migration (e.g., lissencephaly, polymicrogyria, gray matter heterotopia), congenital lung anomalies, hypoplastic left heart, aortic and pulmonic valve stenosis, coarctation of the aorta, renal and bladder anomalies, gastrointestinal anomalies, as well as several skeletal anomalies that may manifest only later in pregnancy [7, 10, 12, 14, 25, 29–32].

Table 13.2 First-trimester detection rates for congenital anomalies

Author	Country	Year	*N*	Approach	Detected anomalies *N* (%)	Additional fetuses with anomalies detected >14 weeks (including second- and third-trimester scans and postnatally) *N* (%)	First-trimester detection rate (%)
Rottem et al. [1]	Israel	1989	141	TV	3 (2.12)	0	100
Cullen et al. [27]	USA	1990	622	TV	33 (5.31)	NA	NA
Rottem and Bronshtein	Israel	1990	1652	TV	40 (2.42)	4 (0.24)	90.9
Achiron and Tadmor [3]	Israel	1991	800	TA and. TV	8 (1.00)[a]	6 (0.75)	57.1
Bonilla-Musolles	Spain	1994	834	TV	27 (3.24)	3 (0.36)	90
Yagel et al. [29]	Israel	1995	536	TV	42 (7.8)	13 (2.4)	76.4
D'Ottavio et al. [31]	Italy	1995	4078	TV	54 (1.3)	34 (0.83)	61.4
Hernadi and Torocsik [30]	Hungary	1997	3991	TA and TV	20 (0.41)	29 (0.73)	40.8
Economides et al. [63]	England	1998	1632	TA + TV	11 (0.67)	6 (0.37)	64.7
Whitlow et al. [64]	England	1999	6634	TA + TV	37 (0.56)	55 (0.83)	40.2
Guariglia and Rosatti [10]	Italy	2000	3478	TV	33 (0.95)	31 (0.89)	51.6
Carvalho et al. [65]	Brazil	2002	2853	TA + TV	29 (1.02)	101 (3.54)	22.3
den Hollander et al. [66]	Netherlands	2002	101	TA + TV	9 (9)	2 (2)	81.8
Drysdale et al. [67]	England	2002	984	TA	5 (0.51)	25 (2.54)	16.7
Taipale et al. [68]	Norway	2004	4513	TV	6 (0.13)	27 (0.59)	18.2
Chen et al. [69]	Hong Kong	2004	1609	TA + TV	14 (0.87)	12 (74.6)	53.8
Becker and Wegner [14]	Germany	2006	3094	TA + TV	72 (2.36)	14 (0.45)	83.7
Saltvedt et al. [70]	Sweden	2006	18,053	TA	74 (0.41)	297 (1.64)	20
Cedergren et al. [71]	Sweden	2006	2708	TA	13 (0.48)	19 (0.70)	40.6
Dane et al. [72]	Turkey	2007	1290	TA + TV	17 (1.32)	7 (0.54)	70.8
Chen et al. [69]	Hong Kong	2008	3949	TA + TV	30 (0.76)	33 (0.84)	47.6
Oztekin et al. [73]	Turkey	2009	1085	TA and TV	14 (1.29)	7 (0.65)	66.6
Ebrashy et al. [7]	Egypt	2010	2876	TA + TV	21 (0.73)	10 (0.35)	67.7
Syngelaki et al. [28]	England	2011	44,859	TA + TV	213 (0.48)	275 (0.61)	43.6
Iliescu et al. [11]	Romania and Greece	2013	5472	TA + TV	67 (1.22)	98 (1.05)	41.1
Bromley et al. [12]	USA	2014	9962	TA + TV	50 (0.50)	130 (1.30)	27.7
Goldstein et al. [21]	Israel	2014	4467	TA + TV	33 (0.74)	28 (1.04)[b]	54.1

TA + TV, transabdominal ultrasonography, followed by transvaginal ultrasonography if adequate views could not be obtained transabdominally; TA and TV, transabdominal followed by transvaginal ultrasonography in all cases; TV, only transvaginal ultrasonography

[a]4/8 anomalies detected only by transvaginal ultrasonography

[b]Ascertainment available for only 60 % of the scanned pregnancies

What Does 3D Ultrasound Add?

3DUS adds the possibility to obtain multiple planes of an anatomical structure from a 3D volume dataset. The elevation plane, in particular, which is perpendicular to the direction of the sound beam, is impossible to obtain using conventional 2DUS. This capability can be particularly advantageous during the first trimester, when manipulation of the vaginal probe is restricted and, therefore, the obtainable planes of section are limited [33]. Another potential benefit,

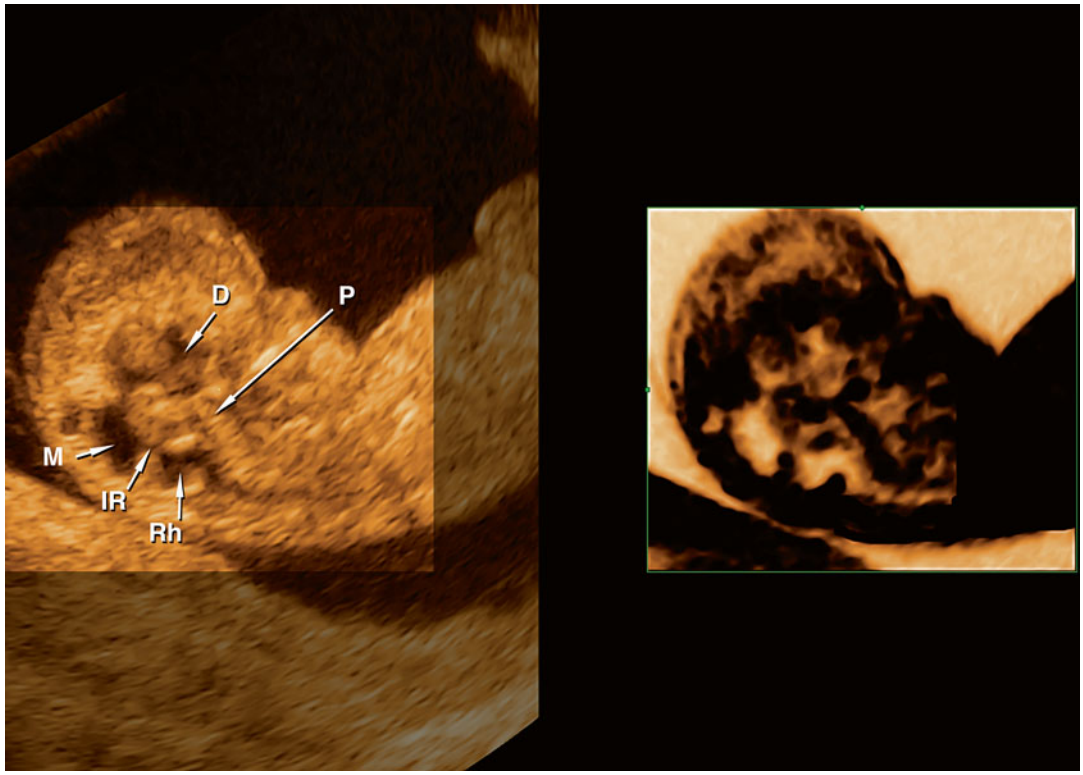

Fig. 13.1 3D rendering of the early cerebral ventricles using inversion mode. *P* pontine flexure, *D* diencephalon (future third ventricle), *M* mesencephalon (future sylvian aqueduct), *IR* isthmus rhombencephali, *RH* rhombencephalic cavity

provided that it can be proved beyond doubt that offline analysis of volume datasets has at least the same level of accuracy as real-time analysis of 2DUS images, is that embryonic exposure to ultrasound can be reduced, since volume acquisition takes only a few seconds and image processing and analysis can be performed offline [34].

Sonoembryology is the term that describes a detailed assessment of the live embryo in vivo by high-resolution transvaginal ultrasonography [33, 35, 36]. Initial publications on sonoembryology relied on images obtained by 2DUS. Since the original work describing the use of a specially designed high-resolution 3D transvaginal probe for reconstruction of small embryonic structures by Blaas et al. [37] in 1995, several investigators have reported on the use 3DUS for volumetric measurement [38, 39], assessment of normal embryonic development and early fetal anatomy [34, 40–46], as well as early prenatal diagnosis of congenital anomalies [42, 47–55].

The best studied organ has been the embryonic brain, with initial studies focusing on volumetry and anatomy of cerebral brain vesicles [37, 38, 56]. Today, exquisite 3D images of the ventricular system can be obtained using commercially available equipment and inversion mode technology (Fig. 13.1), as reported by Kim et al. [42], who obtained 3DUS volumes of the embryonic and early fetal brain by transvaginal ultrasonography in 46 patients examined between 6 and 13 menstrual weeks. Inversion mode was used to reconstruct the early ventricular system. Appropriate reconstructions were possible only for volumes acquired between 7 and 12 weeks. Based on the experience with that work, the authors correctly diagnosed one case of alobar holoprosencephaly at 10 6/7 weeks and one case of early ventriculomegaly at 12 4/7 weeks.

As it is natural to occur with any emerging technologies, several case reports and series have illustrated how 3DUS helped with specific

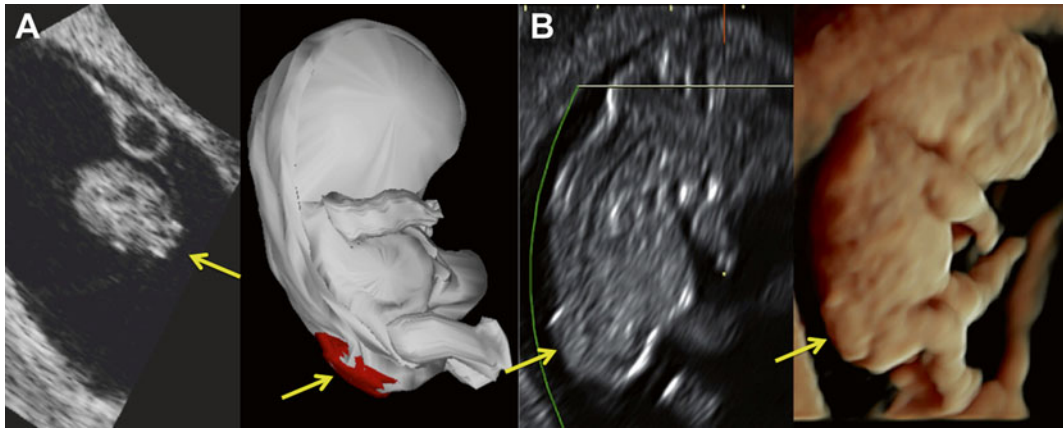

Fig. 13.2 Very early diagnosis of spina bifida by 2DUS and 3DUS at 9 weeks last menstrual period-based gestational weeks. (**a**) Crown-rump length 22 mm. *Left*: horizontal section through the embryonic abdomen. *Right*: three-dimensional geometric reconstruction obtained through manual segmentations; the elevated spinal defect was segmented separately and colored *red*. The *arrows* point at the spinal defect; (**b**) crown-rump length 25 mm. *Left*: sagittal section through the embryonic spine. *Right*: three-dimensional surface rendering showing clearly the myelomeningocele at the embryo's back. The *arrows* point at the spinal defect. Reprinted from Best Practice & Research Clinical Obstetrics & Gynaecology, 28, Blaas HK, Detection of structural abnormalities in the first trimester using ultrasound, 341–53, Copyright 2014, with permission from Elsevier

diagnoses, mainly during the embryonic period [48–51, 57–60]. Among the most interesting are the early detection of a case of spina bifida at 9 weeks with exquisite detail of the defect demonstrated by 3D surface rendered images of the embryonic torso (Fig. 13.2) [49, 58–60], confident diagnoses of cyclopia [50] and proboscis [50, 51] by 3D multiplanar reconstruction at 9 2/7 weeks [50] and 10 6/7 weeks [51] in association with alobar holoprosencephaly, digital casts of the abnormal ventricular system in cases of holoprosencephaly as early as 9 2/7 weeks, conjoined twins at 9 [55] and 10 weeks [57], prune-belly syndrome [58], iniencephaly [45] and frontonasal malformation [61] at 11 weeks, and severe scoliosis associated with omphalocele [58] and encephalocele [45] at 12 weeks.

More recent research efforts have focused on the role of 4DUS with spatiotemporal image correlation (STIC) technology and color Doppler for evaluation of the first trimester fetal heart (Fig. 13.3). Reported visualization rates for normal fetal echocardiographic landmarks are: situs (61–64 %), four-chambers (86–100 %), left ventricular outflow tract (50–91 %), right ventricular outflow tract (64–100 %), three-vessel and trachea view (75–98 %), and pulmonary veins (32–54 %) [17, 18, 62]. In studies that have addressed the issue of visualization rates according to gestational age at the time of examination, improved visualization rates for specific structures such as the aortic root and three-vessel view, and a complete examination of the heart were usually possible only after 12 weeks [18]. Improved visualization rates correlate with higher quality volume datasets (based on lack of motion and sharpness of original images) and volume acquisition using a transvaginal probe [19]. Successful early diagnosis of congenital heart disease has been reported in a few studies, including cases of transposition of the great arteries, tricuspid atresia, Ebstein's anomaly, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, isolated ventricular septal defects, double outlet right ventricle with mitral atresia, hypoplastic left heart syndrome, and atrioventricular septal defects [18–20]. Espinoza et al. [20] reported on a multicentric study in which four international centers with expertise in first-trimester 4D fetal echocardiography were asked to examine 4D volume datasets of normal ($n = 17$) and abnormal fetuses ($n = 16$) without prior knowledge of clinical indications or results of the 2DUS examination. The median (range) accuracy, sen-

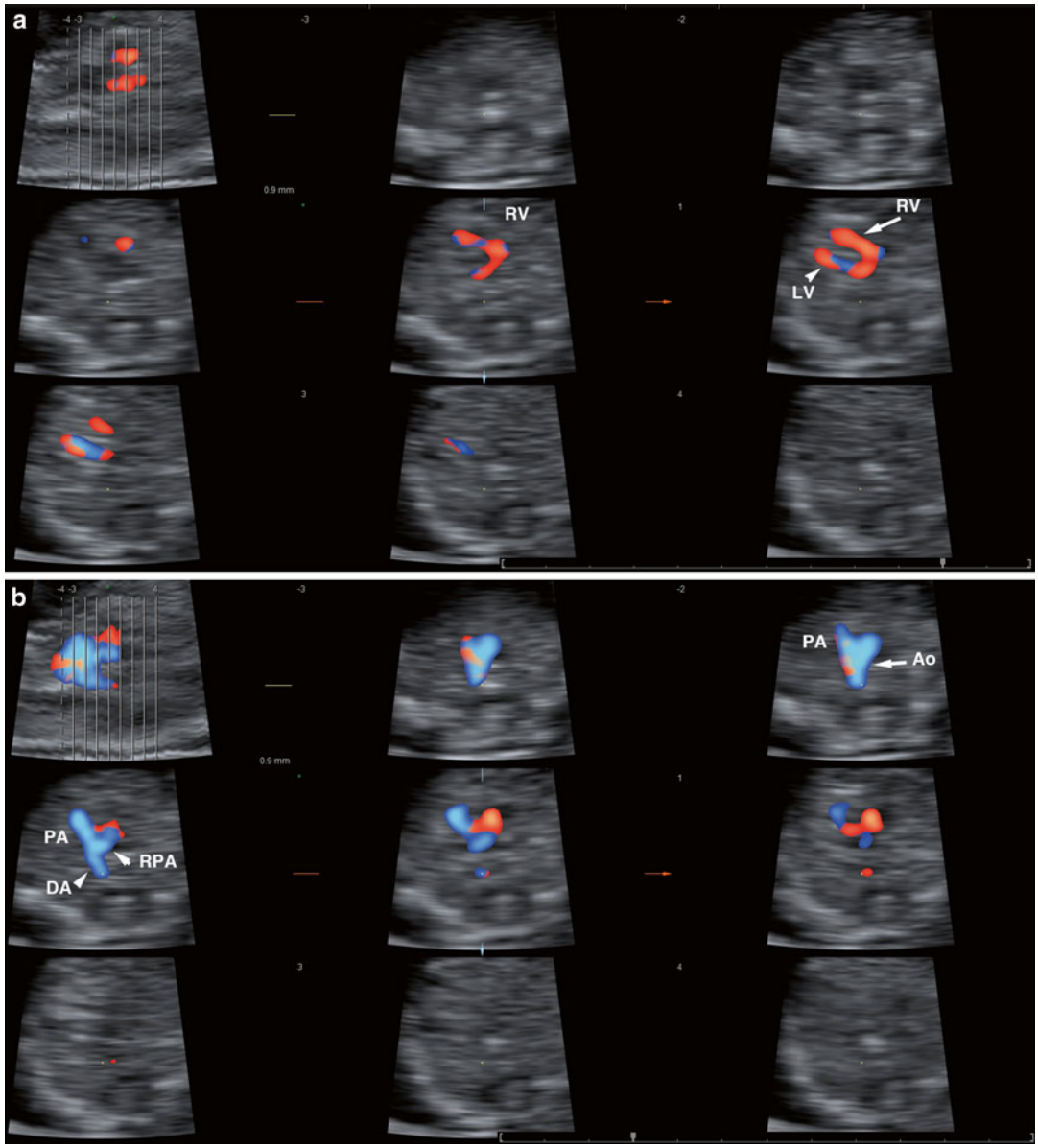

Fig. 13.3 Tomographic ultrasound image of a volume dataset of the fetal heart obtained using transvaginal ultrasonography with color Doppler and STIC technology at 12 weeks. Images are presented in diastole (**a**) and systole (**b**). Note that the aortic root and pulmonary veins are sometimes difficult to visualize in volumes obtained early in pregnancy, as noted in previously published research [17, 18, 62]. *PA* pulmonary artery, *Ao* aorta, *DA* ductus arteriosus, *RPA* right pulmonary artery, *LV* left ventricle, *RV* right ventricle

sitivity, and specificity as well as the positive and negative likelihood ratios, for the identification of fetuses with congenital heart defects were 79 % (77–83 %), 90 % (70–96 %), 59 % (58–93 %), 2.35 % (2.05–9.80 %), and 0.18 % (0.08–0.32 %), respectively. The study showed that experienced examiners can use volume datasets to diagnose congenital heart disease with reasonable sensitivity between 11 and 15 weeks; however, the specificity of 59 % was somewhat disappointing. In the only study that compared the effectiveness of 4DUS with STIC against transvaginal 2DUS

for diagnosis of congenital heart disease, which included 121 fetuses examined by 2DUS and 115 fetuses examined by 2DUS and 4DUS with STIC, the diagnostic accuracy and area under the receiver-operating characteristics (ROC) curve were significantly higher for 2DUS (diagnostic accuracy: 2DUS 94.2 % vs. 4DUS with STIC 88.7 %; area under the ROC curve: 2DUS 0.912 vs. 4DUS with STIC 0.818, $p < 0.05$) [18].

Summary

3DUS is an attractive technology for early evaluation of the human fetus, with several anomalies, usually major, correctly diagnosed by the method, as illustrated by several case reports, small series, and pictorial assays. At this time, there is no evidence that unequivocally supports that 3DUS is either superior to or that it improves the diagnostic accuracy for early detection of congenital anomalies over 2DUS.

More research is needed, comparing actual diagnostic accuracy of offline analysis of a first-trimester volume dataset, without knowledge of the results of the 2DUS before having access to 2DUS images obtained by a technologist or colleague, or direct real-time examination of the patient [60]. Only in this way will there be unbiased data to support an eventual role for 3DUS in the systematic evaluation of first-trimester pregnancies.

Teaching Points

- High-resolution images of the embryo and early fetus can be obtained with transvaginal ultrasonography.
- Several studies demonstrate that early diagnosis of major congenital anomalies is possible by high-resolution transvaginal ultrasonography; however, early ultrasonography is not sufficient to diagnose a significant number of anomalies that may manifest only in the second or third trimesters.
- High-resolution 3D imaging of the embryo and early fetus can be obtained using transvaginal probes equipped with 3D and 4D technology, facilitating understanding of embryonic anatomy in vivo (sonoembryology).
- There is currently no evidence that first trimester 3DUS is superior to or that it definitively improves the detection rates for congenital anomalies compared to 2DUS.

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Multiple Gestations—Multiple Headaches

14

Jacques S. Abramowicz

Introduction

Multiple gestations are often a surprise. When diagnosed, all involved become concerned, future parents and caregivers alike, which explains the title of this chapter. The incidence of multiple births has risen in the last 30 years and comprises today 3 % of all live births in the USA [1] and in the UK [2]. This rise is principally due to the introduction and increasing use of assisted reproduction techniques (ART), specifically in vitro fertilization (IVF) with almost a quarter of these procedures resulting in multiple gestations (mostly twins), when successful [3, 4]. Another factor is the shift in the women age demographics, with maternal advancing age an etiologic factor both by the increased rate of spontaneous multiple gestations, with one-fourth to one-third of the increase in multiple gestations explained solely by the increase in maternal age [5], as well as the need for ART in this population [6]. Twins have, traditionally been classified as dizygotic (DZ), commonly referred to as "non-identical" or "fraternal" or monozygotic (MZ), also called "identical." Genetics have provided new insights that seem to revolutionize our thinking of the twinning phenomenon: there are non-identical MZ twins, there are intermediate forms rather than pure dizygocity or monozygocity and MZ twins may not happen by chance alone [7]. An unchanged fact is that these multiple pregnancies are at increased risks of complications, both maternal and fetal/neonatal. Maternal morbidity—such as miscarriages [8], diabetes [9], hypertensive disorders [10], including preeclampsia [11], preterm labor [12], preterm premature rupture of membranes [13], placental abruption, operative delivery [14], and postpartum hemorrhage [15]—and mortality are greatly increased [16, 17]. The fetuses, in turn, have a much higher rate of spontaneous abortions, genetic anomalies, growth restriction, stillbirth, preterm deliveries (50 % of twins, with 67 % of multiple pregnancies with gestational age [GA] below 28 weeks compared to 26 % of single pregnancies [18]), as well as specific complications in the case of monochorionicity, such as twin-to-twin transfusion syndrome [19]. While multiple pregnancies result in 3 % of live births, they encompass 10–15 % of perinatal death [20]. Among babies born with low birth weight, 23 % are twins. Up to 25 % of most NICU census are the results of multiple gestations and the expenditure for twins is six times that for a singleton newborn [21, 22]. This, naturally, is even higher for higher degree multiple gestations [23, 24]. In an analysis of 11,061,599 singleton, 297,622 twin, and 15,375 triplet gestations, the prospective risk of fetal death at 24 weeks was 0.28 per 1000, 0.92 per 1000, and 1.30 per 1000,

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respectively [24]. Furthermore, 4.6–10 % of all cerebral palsy cases occur in twins, which is more than four times the observed frequency in the general population [25]. The rate of multiple birth in the populations increased from 1.9 % in 1980 to 2.4 % in 1990, and the proportion of multiples among CP infants increased from 4.6 % in 1976 to 10 % in 1990. Multiples have a four times higher rate of CP than singletons (7.6 vs. 1.8 per 1000 live births, relative risk [RR] 4.36; 95 % confidence interval [CI] 3.76–4.97) overall [22, 26]. It is interesting to note that the risk is not related to preterm birth only. A threefold increase in CP is found in neonates from multiple versus singleton pregnancies [27]. These complications become even more prevalent in higher order multiple gestations such as triplets, quadruplets, or higher [20, 28].

Embryology

A major reason for the recent increase in multiple pregnancies is ART and the use of fertility enhancing treatments. In the USA twin births increased from about 1/50 infants in 1980 to 1/30 infants in 2009 [29]. Similar trends have been described in multiple reports from other parts of the world [30]. The two commonly cited reasons are that ovulation inducing agents increase the likelihood of more than one ovulation (Fig. 14.1) and multiple embryos are transferred in in vitro fertilization (IVF), all resulting in DZ twins [31]. This has led various societies, involved with reproductive endocrinology and infertility, to regularize the optimal number of embryos to transfer [32]. It appears, however, that the risk of embryo cleavage, resulting in monozygotic twins, is also increased in IVF [33, 34]. Genetic factors, rather than the procedure itself, are suspected to be the basis for this occurrence [34].

Embryological development of the fetus is addressed in details in Chap. 2 of this book. Multiple gestations can be the result of a single oocyte being fertilized by a single spermatozoon with splitting of the resulting zygote at various times (monozygotic [MZ] twins) or multiple oocytes (two or more), each fertilized by its own spermatozoon, resulting in two or more zygotes (dizygotic twins [DZ], or higher degree multiples). Dizygotic twins are more common (70 %), and are also known as "fraternal twins" since,

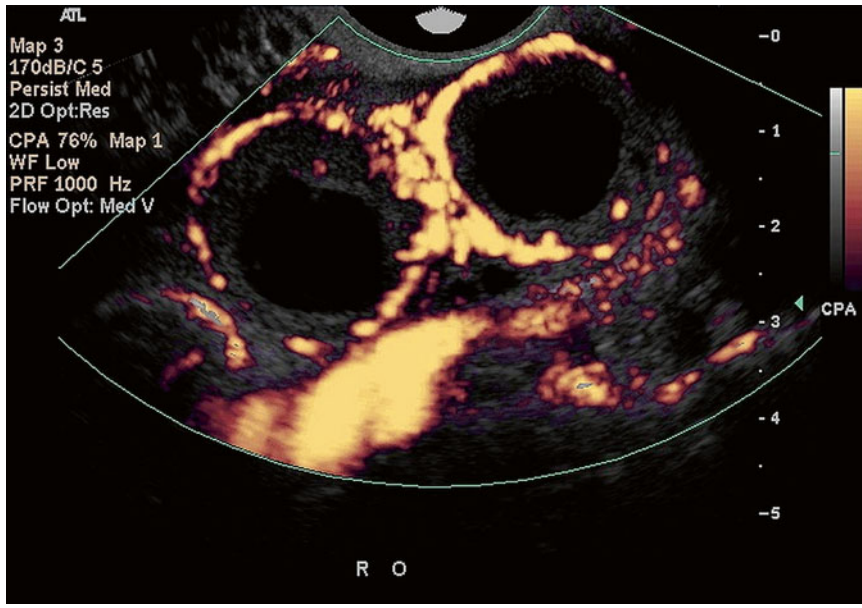

Fig. 14.1 Multiple corpora lutei. This is indicative of multiple follicular ovulation. Multiple corpora lutei can be a sign of a dizygotic pregnancy; however, it is also frequently seen with the use of fertility-enhancing medications

genetically, the two zygotes that resulted are as different as two regular siblings (e.g., opposite genders). The incidence of DZ twins increases with maternal age, parity, ovulation induction and they are more common in some families, with mothers of DZ twins reporting significantly more female family members with DZ twins than mothers of monozygotic twins. Maternal factors such as genetic history, advanced age, and increased parity are known to increase the risk of DZ twins [35]. New findings indicate some women may have a genetic predilection to conceive twins, specifically insertion/deletions and missense alterations in the growth differentiation factor 9 (GDF9) sequence in mothers of twins [36, 37]. Rates of DZ twins have a geographical variation with some countries/continents such as South and South East Asia as well as Latin America exhibiting low prevalence, e.g., 6–9 twin sets per thousand births [38], and rates being much more common in some ethnicities, such as in Nigeria, where the Yoruba have the highest rate of twinning in the world, at 45–50 twin sets per 1000 live births, possibly due to high consumption of a specific type of yam containing a natural phytoestrogen [39]. Dizygotic twins will always be dichorionic–diamniotic (DCDA). Monozygotic twins are known as "identical twins" since they originate from a single zygote and are thus genetically identical (with exceptions, see below). They comprise 30 % of twins and their incidence is sporadic, with no family predilection and with a rate similar throughout the world (1:250 pregnancies). In MZ twins, the time of splitting will determine placentation, chorionicity and amnionicity (see below, placentation). The prevalence of females compared to males increases progressively from a relatively equal prevalence in singletons to a clear preponderance in conjoined twins.

Diagnosis

Before the development of ultrasound, twins were often diagnosed at birth, after the delivery of one neonate. In fact, a multiple gestation was clinically suspected in only 25–50 %. In the famous Routine Antenatal Diagnostic Imaging with Ultrasound Study (RADIUS), 38 % of twins were recognized after 26 weeks and 13 % were not diagnosed until delivery [40]. In the Helsinki Ultrasound Trial, 25 % twins were not recognized until 21 weeks [41]. These two studies, however, were not really about first trimester ultrasound but rather about scanning at mid-trimester (16–24 weeks). The diagnosis should be obtainable, with ultrasound, from very early in gestation. When ultrasound is performed for an indication (e.g., the uterus is larger than expected), the accuracy is about 75 %. When ultrasound is performed routinely, this climbs to 90 % [42], with better outcomes in women known to carry multiple gestations [43]. The first ultrasound indication of a multiple gestation may be the presence of multiple corpora lutei (see Fig. 14.1). While routine ultrasound is still not the official rule, as recommended in low risk pregnancies by the American College of Obstetricians and Gynecologists (ACOG), the American College of Radiology (ACR) or the American Institute of Ultrasound in Medicine (AIUM), the advantages of a policy of routine scanning in the first trimester include, among others, the early detection of multiple gestations, allowing for early determination of chorionicity and amnionicity [44, 45]. Another clear advantage is accurate assessment of gestational age (GA). When ultrasound is ordered "to date" the pregnancy, in cases of unknown or unclear last menstrual period, fetal biometry is used to determine GA. In twins, however, there may be growth discordancy, for instance with one twin measuring 1 week more than the other. The published literature does not provide evidence-based data on whether dating should be based on the smaller twin, the larger or an average. It is important, however, to avoid missing early growth restriction in one twin, thus, the majority will date the pregnancy based on biometry of the larger twin [46]. An important consideration is whether growth nomograms for singleton gestations can be used for twins or higher order gestations [47]. It appears that during the first trimester, there are no major differences in fetal biometry between singleton and multiple pregnancies [46]. Hence, crown-rump-length (CRL) curves

published for singletons may be used in the assessment of twins and triplets [48, 49]. Furthermore, there is no difference in placental mass between singletons, monochorionic (MC) and dichorionic (DC) twins and trichorionic triplets between 11 and 13 6/7 weeks [50]. Growth curves for singletons may be used in the assessment of biometry in twins until approximately 34 weeks GA [51]. For triplets, the upper limit may be lower, e.g., 25 weeks [52].

Placentation

Determining the number of chorionic sacs is important because prognosis is much better in DC than MC twin pregnancies [53]. Mortality (stillbirth, perinatal, and neonatal death) is 3–4 times higher in MC twins [53–58]. The major reason is the presence of vascular anastomoses between the two placental circulations [59–61]. They are at risk of twin-to-twin transfusion syndrome or TTTS [62–66], twin anemia–polycythemia syndrome or TAPS [67–69], twin reversed arterial perfusion or TRAP syndrome [70, 71], unequal placental sharing with discordant twin growth or selective intrauterine fetal growth restriction [72], and, if also monoamniotic (MA), cord entanglement with the added risk of demise of one twin and embolization of thromboplastin from the demised fetus to the healthy twin [73–75]. Additionally, there is the risk of conjoining, an event occurring in 1/50,000 births [76]. Mortality is 8–10 % in DCDA, 25 % in MCDA, 50–60 % in MCMA, and perhaps 90 % in conjoined twins [77–79] with fetal loss under 24 weeks, 1.8 % in DC twins, and 12 % in MC twins [53].

As described above, approximately 70 % of twins delivered and conceived naturally, result from the fertilization of two independent oocytes, i.e., dizygotic (DZ) twins; the remaining 30 % are the result of the division of a single zygote, i.e., monozygotic (MZ) twins. Interestingly, the rate of MZ twins is three times higher in pregnancies conceived with the help of ART, compared to spontaneous conceptions [80, 81]. If the division of the zygote occurs at the two-cells stage (0–4 days), before the morula stage, this results in two morulas, two blastocysts, two chorions, and two amnions (dichorionic–diamniotic or DCDA placentation), about one-third of monozygotic twins. In about two-thirds of monozygotic twins, the split occurs after the morula stage (4–7 days) and the single morula split will result in MCDA placentation. If it occurs at 7–14 days, the embryonic disc was already formed and the result will be two embryos in the same sac (MCMA). If after day 13–14, conjoined twins will result. A combination of both may also exist, when one of two dizygotic twins splits, in a monozygotic fashion, resulting in various combinations of chorionicity and amnionicity.

Ultrasound plays an important, if not the major, role in the determination of chorionicity and amnionicity early in pregnancy [44, 72, 82–94]. Various algorithms themes can be used, based on what is the known (or assumed) gestational age [95–97]. With appropriate training, reproducibility of the results has been shown to be excellent [98].

From 4 to 6 weeks, the number of sacs determine the chorionicity: two sacs means twins are DC (Fig. 14.2).

From 6 to 8 weeks, if the number of sacs is the same as the number of yolk sacs and the number of fetuses, this is a DCDA pregnancy. If the pregnancy is MC, two fetuses will be visualized within the sac and the number of yolk sacs will help distinguish between DA and MA placentation. Observing two yolk sacs or two clear amniotic cavities (Fig. 14.3) allows one to make the diagnosis of diamniotic twins [99]. Visualization of two fetal poles with a single yolk sac is diagnostic of monoamnionicity (Fig. 14.4). Once the membranes can be visualized, ultrasound imaging can distinguish between MC and DC twin pregnancies with more than 90 % accuracy [93]. The "twin peak," also called lambda sign, at the level of the attachment of the chorionic membranes to the placenta is formed by projection of the trophoblast from a fused dichorionic placenta between the layers of the membranes and indicates a DC twin pregnancy (Fig. 14.5), with 100 % accuracy, while the "T sign" at the site where the thin inter-twin membrane composed of

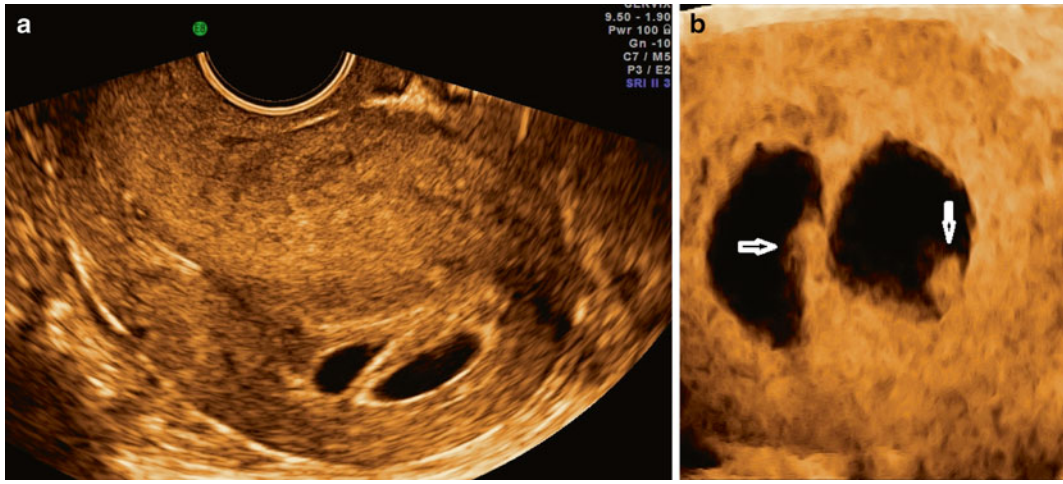

Fig. 14.2 Dichorionic diamniotic twins, 5 weeks. (**a**) In this retroverted uterus, two separate sacs are distinguished at 5 weeks. (**b**) 3D image a few days later demonstrates the presence of two fetal poles (*arrows*)

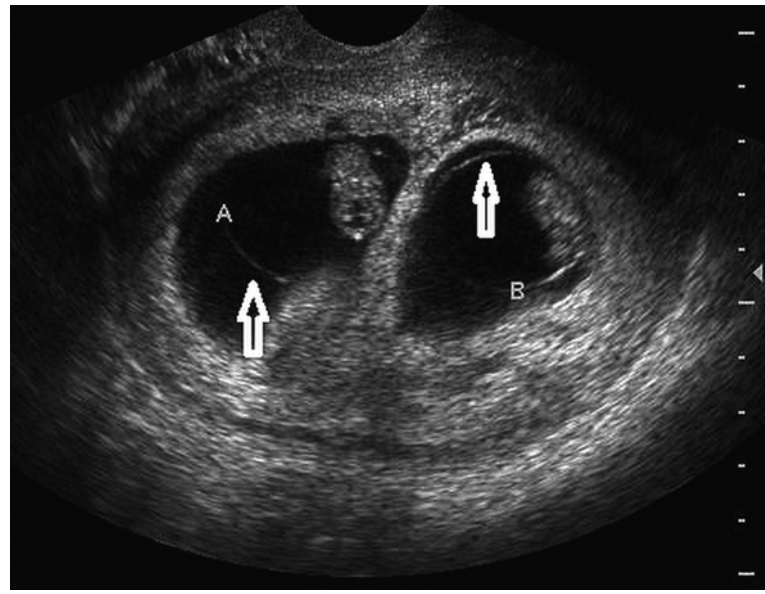

Fig. 14.3 Diamniotic twins. Two clearly separate amniotic cavities are distinguished. Amniotic membranes are marked by *arrows*

two amnions with no chorions leaves the placenta at a 90° angle (Fig. 14.6) indicates a monochorionic–diamniotic (MCDA) twin pregnancy [100]. In a study of 55 cases, sensitivity of the twin-peak sign for dichorionicity was 94 %, specificity 88 %, positive predictive value 97 %, and negative predictive value 78 % [101]. In another study of 506 DC and 154 MC twin pregnancies, between 11 and 14 weeks of gestation, use of the twin-peak and T signs and the number of placentas had sensitivity of 100 % specificity of 99.8 % for monochorionicity, with only one DC pregnancy incorrectly assigned as MC [102].

From 8 to 14 weeks, the number of placental masses and/or the lambda or T sign can be assessed, as above, but at that stage, membrane thickness can also be analyzed [88]. A dichorionic membrane is typically well defined and easy to visualize with ultrasound. It consists of four layers (i.e., two layers of both amnion and

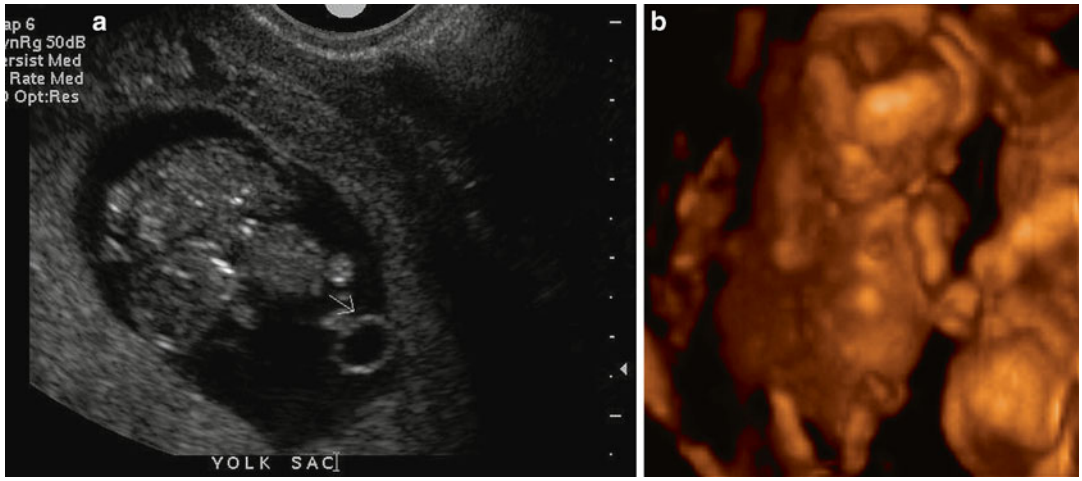

Fig. 14.4 Monoamniotic twins, 6 weeks. (**a**) Two fetal poles are visualized and only one yolk sac is demonstrated (*arrow*). (**b**) At 10 weeks, three-dimensional ultrasound demonstrates both twins in a single sac, with no intervening membrane

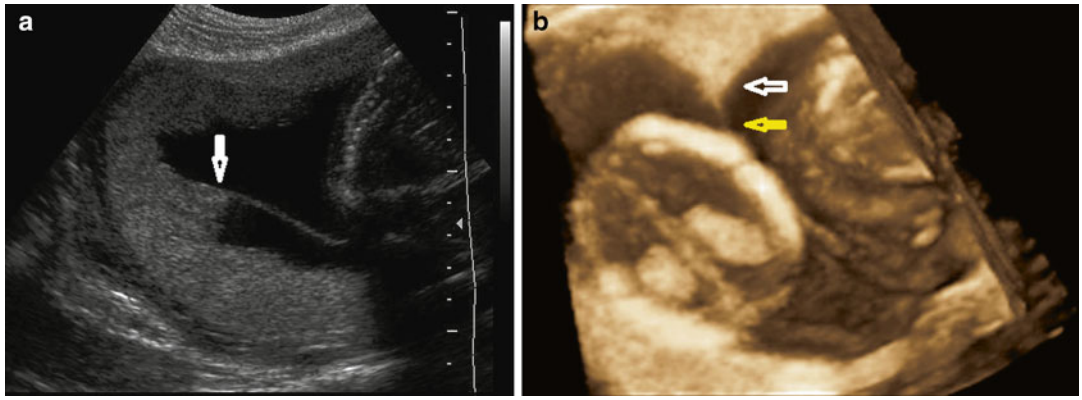

Fig. 14.5 Twin peak or lambda sign. Two-dimensional B-mode (**a**) and three-dimensional (**b**) ultrasound of a dichorionic diamniotic pregnancy. The *white arrows* point to where the "peak" is formed from the two placentas abutting. The inter-twin membrane (*yellow arrow*) appears thin. If the lambda sign was absent, accurately determination of chorionicity would be challenging

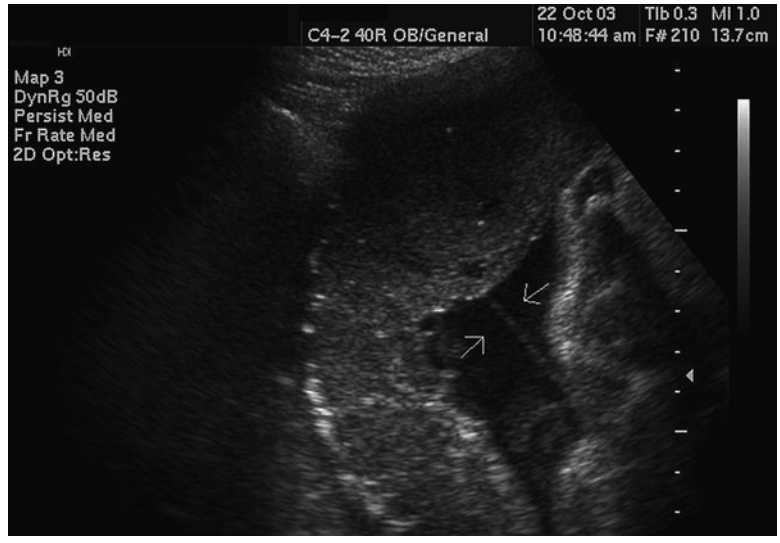

Fig. 14.6 T sign. The *arrows* point to a thin membrane, connecting to the placenta at a right angle, forming the *letter T*. This is diagnostic for a monochorionic placentation

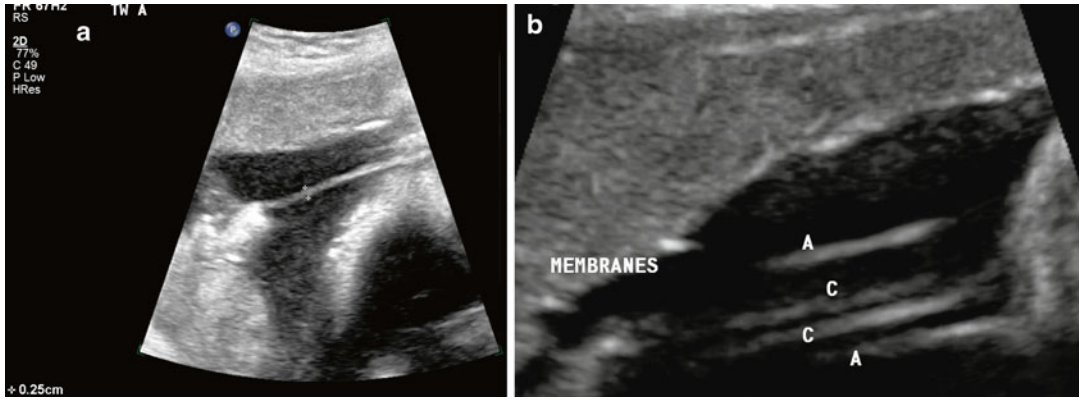

Fig. 14.7 Dichorionic diamniotic membrane. (**a**) Membrane measures more than 2 mm in width. (**b**) Four layers (two chorionic and two amniotic membranes) can be visualized

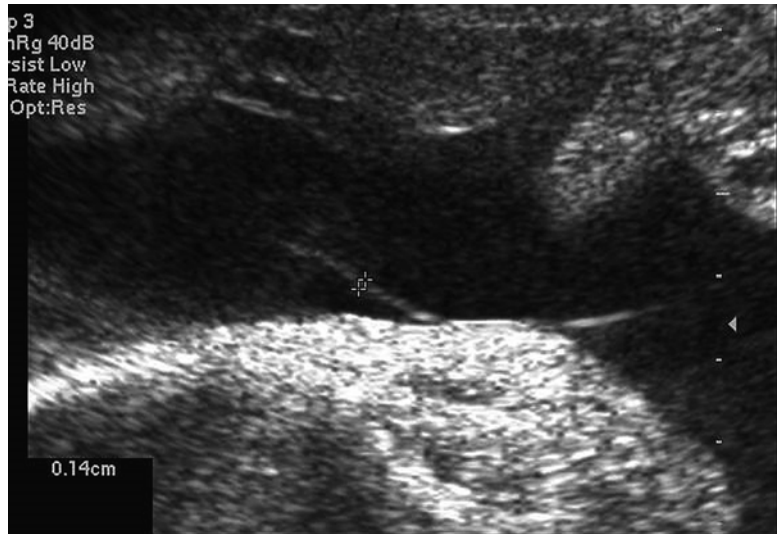

Fig. 14.8 Monochorionic diamniotic membrane. The membrane is thin (1.4 mm) and elusive

chorion) and its width will be greater than 2 mm (Fig. 14.7). The presence of a thick dividing membrane indicated a dichorionic–diamniotic gestation in 38 (90 %) of 42 cases in which it was identified [103]. The number of dividing membranes can also, occasionally, be counted: four means DCDA (Fig. 14.8), two means MCDA [95].

For women presenting *after 14 weeks 0 days*, all of the above features should be used and, in addition, evaluation of fetal gender, since discordancy would, obviously, signify dizygocity [104]. In the second and third trimesters, membrane thickness is much less useful [105].

If transabdominal views are poor because of elevated BMI or retroverted uterus, transvaginal ultrasound is recommended. In a study by Bora and colleagues [106], chorionicity and amnionicity were documented in 67 viable twin pregnancies at both 7–9 and 11–14 weeks' gestation. There was agreement in the chorionicity and amnionicity reported at each of the two scans in 65 out of 67 (97 %) cases. Of the DCDA pregnancies reported at 7–9 weeks, 53 out of 54 (98 %) were confirmed at the 11- to 14-week scan and one (2 %) was found to be MCDA. At birth, however, these twins were of different sex, confirming DCDA twins as initially diagnosed at

7–9 weeks. Of the 12 pregnancies diagnosed as MCDA at 7–9 weeks, all were found to be MCDA at the 11- to 14-week scan. In the (rare) case when chorionicity cannot be established, management should be based on the assumption that the gestation is monochorionic, until proved otherwise. After ultrasound diagnosis and characterization of twins, the risk of spontaneous loss of both fetuses before 22 weeks of gestation is significantly higher in MC than in DC pregnancies, and is significantly higher in MCMA pregnancies than in MCDA pregnancies [107]. Hence, no ultrasound report on twins should be considered finalized without details of the type of placentation [108]. Another sign has been described in triplet pregnancy: the ipsilon zone, the junction of the three interfetal membranes with 100 % success in determining chorionicity in 19 sets of triplets [109].

Another important role for ultrasound in multiple gestation is observation of the umbilical cord insertions in the placenta. Abnormal cord insertions such as marginal and velamentous insertions are much more frequent in multiple gestation (Fig. 14.9). In addition, single umbilical artery is also much more frequent in twins [110, 111].

Complications

Several complications are unique to multiple gestations: vanishing twin, death of one fetus, discordant fetal growth, discordance for genetic/structural anomaly, and partial mole. Some will only be found in monochorionic gestations (TTTS, TAPS, TRAP) while conjoined twins and cord entanglement are specific for MCMA gestations, which have been called "the most precarious of twin pregnancies" [112].

Vanishing Twin

This refers to a phenomenon, first described by ultrasound in 1982 [113], where, after documentation of multiple fetal heart activity, one embryo may not be visualized in a subsequent ultrasound. In fact, among gestations that start as twins, approximately one third will ultimately result in singletons and about 10 % will result in no fetuses. Multiple pregnancies may constitute more than 12 % of all natural conceptions, of which only about 2 % survive to term as twins and about 12 % result in single births [114].

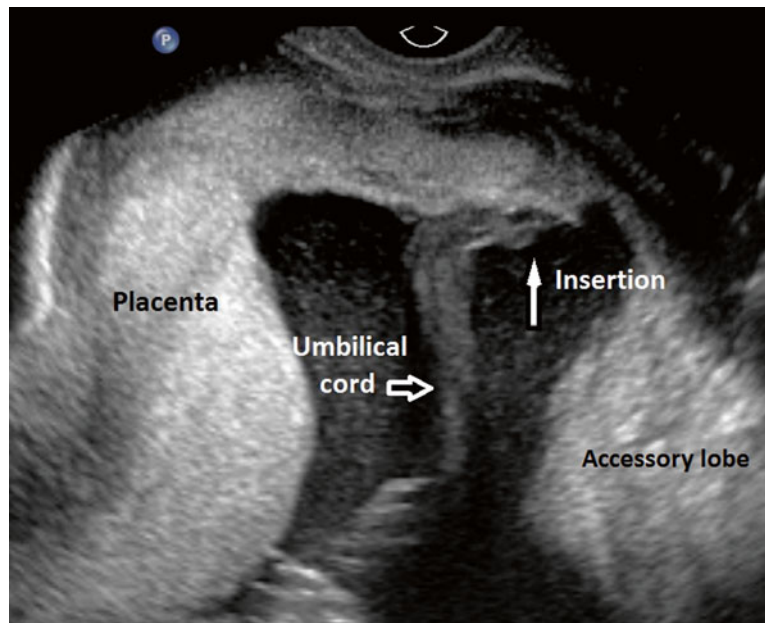

Fig. 14.9 Velamentous insertion of the cord in a twin pregnancy

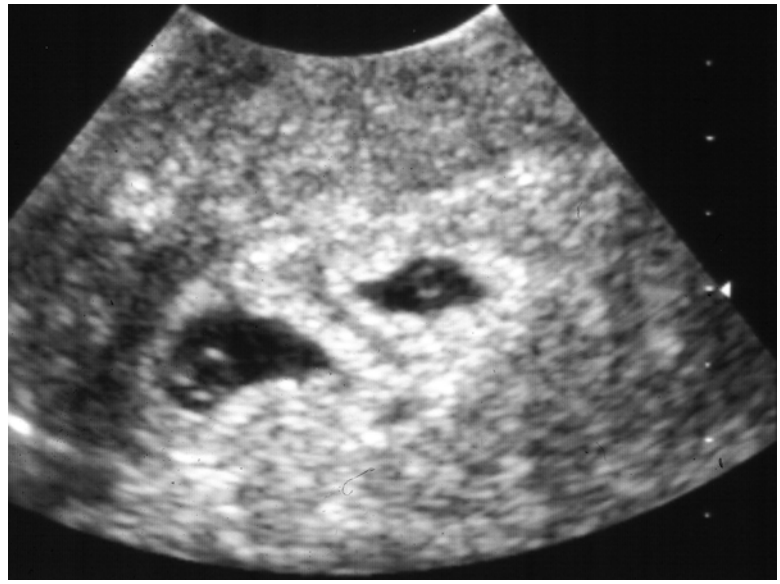

Fig. 14.10 Vanishing twin. One sac is much smaller and contains a very small yolk sac. If scanned at a later date, this would probably be missed

In pregnancies diagnosed as twins prior to 7 weeks of gestation spontaneous reduction of one or more gestational sacs and/or embryos occurred before the twelfth week of gestation in 36 % of twin, 53 % of triplet, and 65 % of quadruplet pregnancies [115]. As evident from the above numbers, the phenomenon is even more common in higher order multiples [116], occurring in up to 50 % of triplet pregnancies with a triplets delivery rate of 47.4 % among 38 pregnancies diagnosed around 7 weeks with triplets, whereas 31.6 % delivered twins, 18.4 % delivered singletons, and only one patient miscarried all three cases [117]. The ultrasound diagnosis includes complete disappearance of a previously clearly demonstrated gestational sac and/or embryo or sonographic findings, indicating a failed pregnancy: sac smaller than expected, with irregular margins, crescent as opposed to sphere shaped or incomplete trophoblastic ring [118] (Fig. 14.10). Despite the fact that some patients will have vaginal bleeding, prognosis for continuation of a pregnancy in which the vanishing twin phenomenon occurred, is excellent, regardless of the type of chorionic placentation. Birth weight, however, is lower for survivors of the vanishing twin syndrome [119]. One of the problems when this occurs is that serum aneuploidy screening may be affected with elevated levels of several analytes. In a recent study of 174 pregnancies with a vanishing twin, compared with control pregnancies, pregnancy associated plasma protein A (PAPP-A) increased by 21 % ($p=0.0026$), alpha-fetoprotein (AFP) increased by 10 % ($p<0.0001$), and dimeric inhibin A (DIA) increased by 13 % ($p=0.0470$) in pregnancies with a vanishing twin. Unconjugated estriol and total human chorionic gonadotrophin were not significantly changed in these pregnancies [120]. Errors may also occur with noninvasive cell-free fetal DNA testing, specifically with sex determination [121]. Death of one fetus is somewhat similar to the vanishing twin phenomenon but generally occurring later in pregnancy [122]. Single fetal demise occurs in 3.7–6.8 % of all twin pregnancies and considerably increases the complication rate in the co-twin including fetal loss, premature delivery, and end-organ damage [123, 124]. In a large review of the literature, Ong and colleagues determined that following the death of one twin, the risk of a DC and MC co-twin demise was 4 and 12%, respectively. The risk of neurological abnormality in the surviving DC and MC co-twin was 1 and 18 %, respectively. The odds of MC co-twins intrauterine death was six times that of DC twins [122]. The issue of

neurological damage in the surviving twin is particularly relevant to parents and clinicians. When death of one of a set of MC twins occurs, the surviving twin is at risk of major morbidity and mortality. This is thought to be due to exposure to thromboplastin, originating in the dead fetus circulation and reaching the surviving twin placental vascular connections and causing thromboembolic phenomena in various organs, particularly the brain [125] and DIC. Anomalies most commonly described in the literature all seem to involve some vascular accident component and include porencephalic cyst, hydranencephaly, microcephaly, intestinal atresia, gastroschisis, limb amputation, and aplasia cutis [126]. Another possible mechanism is hypovolemic-related hypotension, secondary to extensive blood loss from the surviving twin into the lower resistance circulation of the deceased twin. Fetus papyraceus is a rare condition with intrauterine demise of one twin [127]. The estimated frequency is 1:12,000 live births with an incidence of 1:184–1:200 twin pregnancies [128–130] but may occur more commonly in higher order gestations. Water content and amniotic fluid of the dead twin is reabsorbed and the fetus is compressed and mummified, resembling Egyptian parchment paper, hence the name. It is incorporated into the placenta of the surviving twin and is retained for various periods of time, including until delivery (preterm or term) of the surviving twin when it can be looked for in the placenta, after delivery [131].

Growth Restriction and Differential Growth

In the first and second trimesters, the growth rate of normal twins is not significantly different from that of singletons. Any etiology of restricted growth in singletons may affect both twins equally or one, rather than the other, a condition designated as differential growth. Generally, in these cases, one twin is appropriate for GA (AGA) and one is small for GA (SGA). If the differential growth is secondary to one fetus being AGA and the other large for GA (LGA), this is not associated with major complications (at least until labor and delivery). The two major mechanisms for differential growth are placental specific dysfunction and genetic factors. In DZ twins, the SGA twin is often simply constitutionally small and different from his/her co-twin as two siblings might be. Another possible etiology is velamentous insertion of the cord of the small fetus since, as mentioned earlier, this entity is more common in multiple gestations [110] and is known to possibly be associated with intrauterine growth restriction [132], maybe due to disadvantageous competition for nutrients [133–136]. In addition, both fetuses may be SGA for placental or genetic reasons. In early pregnancy differential growth may be detected by a difference in crown-rump length (CRL). This trend may start very early [137]. A smaller than expected CRL is more commonly associated with chromosomal anomalies than a normal CRL [137–140]. Aneuploidy by chorionic villus sampling was 4.3 % in a group of singletons with smaller than expected CRL and 1.7 % in controls ($p<0.004$) among 3194 chorionic villus sampling procedures, with 277 (8.7 %) fetuses with CRL smaller than expected by at least 7 days [138]. This association was demonstrated in a study of 159 twin pregnancies. Crown-rump length discordance of more than 10 % was associated with a significantly higher incidence of fetal anomalies (22.2 vs. 2.8 %; $p=0.01$) [141]. Other outcomes, such as fetal loss are also worse with a 10 % discordance or more [142, 143], even in euploid fetuses [144]. In a large meta-analysis of 17 studies, twin pregnancies with CRL discordance ≥10 % were at significantly higher risk of perinatal loss (RR = 2.80, fetal loss at ≥24 weeks (RR = 4.07), BW discordance (RR = 2.24) and preterm delivery at <34 weeks (RR = 1.49) but not of fetal loss at <24 weeks [145]. Before 8 weeks, more than 3-mm difference is associated with 50 % risk of demise of smaller twin [146]. Such discordant growth is not always associated with poor outcome [65] and prediction of outcome based on this difference is less than optimal [147] but inter-twin CRL difference greater than 10 % increases the risk for discordant fetal growth or TTTS while CRL difference of less than 10 % carries an excellent prognosis in terms of perinatal

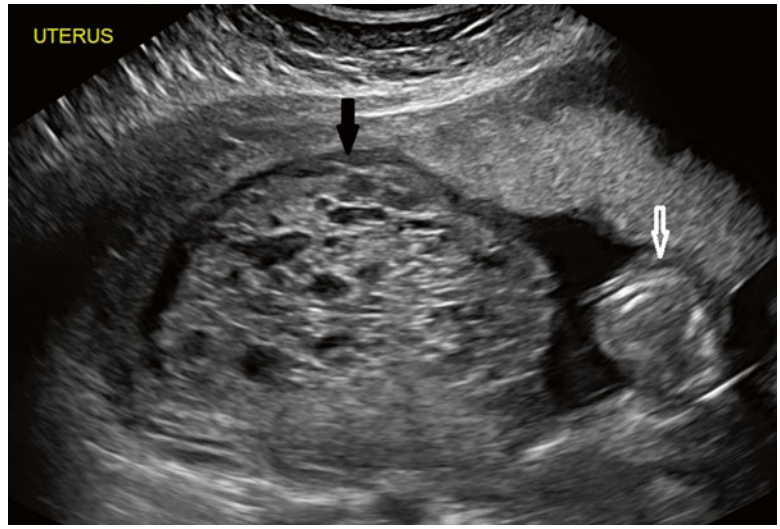

Fig. 14.11 Concomitant mole. Typical appearance of the placenta (*black arrow*). Fetal parts can be distinguished on the right (*white arrow*)

outcome [148]. Growth discrepancy may also be found when both fetuses are AGA but one is significantly smaller than the other. The risk for adverse perinatal outcomes in these cases exists for monochorionic, but not dichorionic, twins [149]. Later in pregnancy (second and third trimesters), various definitions are used: estimated weight of one twin below the tenth percentile, abdominal circumference difference or growth discordance in estimated twin weights greater than 25 % [111, 150]. This aspect is beyond the scope of this book.

Discordance for Genetic/Structural Anomaly

See below, Screening for Genetic and Morphologic Abnormalities.

Complete Hydatidiform Mole and Coexisting Fetus

This is another rare "twinning" event with a normal fetus developing in the presence of a complete hydatidiform mole [151]. The incidence in 1:20,000–1:100,000 pregnancies [152] (Fig. 14.11). If the pregnancy is maintained, management is complicated and women should be followed in a high-risk obstetrics unit. Risks include fetal loss, preeclampsia and persistent gestational trophoblastic disease in over one-third of the cases [153, 154] but delivery of a healthy baby is not impossible, in approximately 50 % of cases [154, 155].

Complications Specific for MC Twins

There is, often, unequal sharing of the placenta, which may cause grave problems: discordant fetal growth with IUGR, metabolic compromise and death [156]. In addition, chronic unidirectional blood shunting through placental vascular anastomoses may occur and result in TTTS or twin reverse arterial perfusion [TRAP] and death). Furthermore, for MCMA twins, additional risks include conjoined twinning and cord entanglement. Risk of cerebral injury and subsequent cerebral palsy is seven times higher than in DC, most likely secondary to vascular anastomoses. If TTTS is present, this risk climbs to 21 % [56, 126]. After single intrauterine demise it is up to 18 % [157–159].

Twin-to-Twin Transfusion Syndrome (TTTS)

Twin-to-twin transfusion syndrome is one of the most serious complications of monochorionic

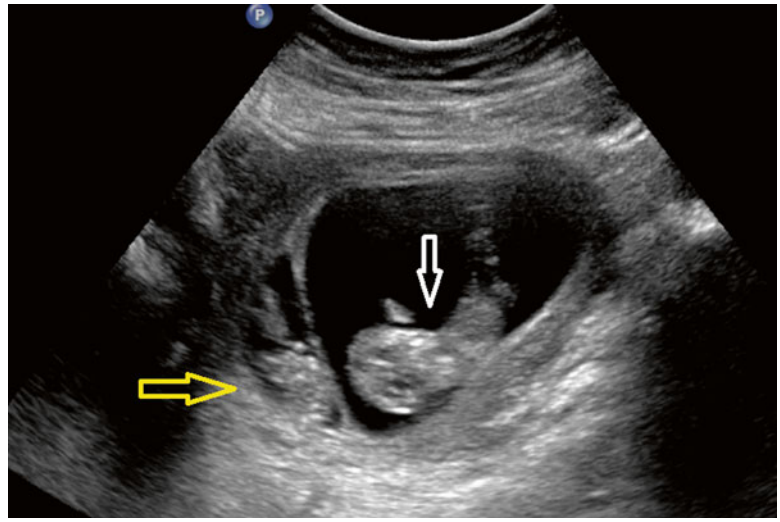

Fig. 14.12 Early signs of TTTS, 10 weeks. Clear difference in size and amount of amniotic fluid between donor (*yellow arrow*) and recipient (*white arrow*)

multiple gestations that occurs in 10–15 % of MCDA twin pregnancies [19]. It is associated with a high risk of fetal/neonatal morbidity and mortality, close to 100 % if not diagnosed and managed [160]. Surviving fetuses are at risk of severe cardiac, neurologic, and developmental disorders. The diagnosis of TTTS requires two criteria: (1) the presence of a MCDA pregnancy; and (2) the presence of oligohydramnios (defined as a maximal vertical pocket of <2 cm) in one sac, and of polyhydramnios (a maximal vertical pocket of >8 cm) in the other sac [64]. Typically this syndrome is suspected when discordant fetal size is present, associated with polyhydramnios in the larger twin and oligohydramnios in the smaller twin of a MCDA pregnancy (Fig. 14.12). Changes in amniotic fluid volume are often the first sign, although CRL and nuchal translucency (NT) differences can also be seen, early in gestation [55, 161]. First trimester abnormal Doppler velocity in the ductus venosus (absent or reversed a-wave) has been associated with increased risks of chromosomal abnormalities, cardiac defects and fetal deaths [162] (Fig. 14.13). Differences in ductus venosus Doppler waveforms between twins has also been described as an early warning sign for subsequent development of TTTS [162, 163]. The etiology is unbalanced vascular anastomoses between the two placentae, arteriovenous (AV), arterioarterial (AA), venoarterial (VA), or venovenous (VV). While AA and VV anastomoses are on the surface of the placenta, AV and VA are deeper in the placental substance. Connections between the two circulations exist in virtually all MC placentation but TTTS develop in only 10–15 %, secondary to hemodynamic imbalance, a phenomenon that is not entirely explained [63]. In 150 pairs of MCDA twins, TTTS occurred predominantly in the presence of AV-anastomoses without compensating superficial AA-anastomoses ($p = 0.005$) and occurred more frequently in the presence of velamentous cord insertion [60]. There is relative hypovolemia in the smaller twin (donor) who releases vasopressin and renin–angiotensin, resulting in oligohydramnios. If this is extreme, the amniotic membrane becomes tightly adherent to the fetal body, resulting in an immobilized "stuck twin." The other twin (recipient) becomes hypervolemic, which results in release of atrial natriuretic peptide (ANP) from the enlarged heart as well as brain natriuretic peptide (BNP). Release of these (natriuretic) hormones results in polyuria and polyhydramnios. In the recipient twin, hypervolemia and increased levels of renin and angiotensin (coming from the donor twin through transplacental crossing) result in cardiomegaly, hypertrophy, particularly of the right side and cardiomyopathy. Diastolic myocardial dysfunction occurs early in the pathophysiology of TTTS [164] and, together with

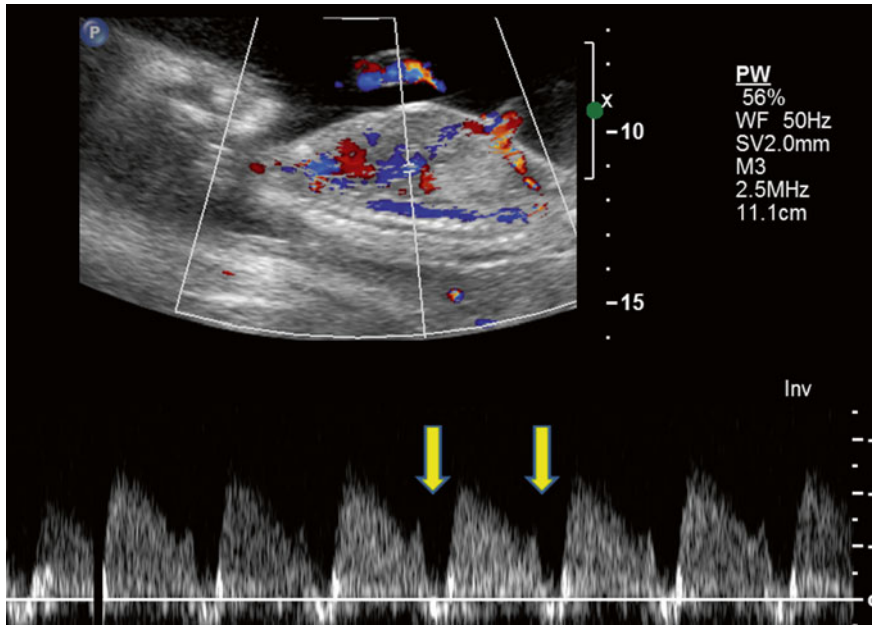

Fig. 14.13 Ductus venosus Doppler velocimetry in TTTS. Reversed a-wave is evident (*arrow*). This is a sign of cardiac failure in the recipient

cerebroplacental redistribution precede findings of overt cardiomyopathy [165]. Further deterioration occurs secondary to venous hypertension with development of hydrops. During the second trimester Quintero's stages are often used to describe the severity of the condition [166].

Twin Anemia–Polycythemia Syndrome (TAPS)

TAPS is a form of TTTS, characterized by large inter-twin hemoglobin differences in the absence of amniotic fluid discordances, as opposed to twin oligo-polyhydramnios sequence or TOPS [167]. It may occur spontaneously in up to 5 % of monochorionic twins and may also develop after incomplete laser treatment in TTTS cases [168]. The etiology is probably few, minuscule AV placental anastomoses (diameter <1 mm) with a slow blood transfusion from donor to recipient, leading gradually to very high hemoglobin (Hb) levels in one twin and very low levels in the second one [167]. Diagnosis may be arrived at by finding discordance in fetal middle cerebral artery peak systolic velocity (MCA-PSV) measurements. Perinatal outcome is difficult to evaluate, since the literature contains mainly case reports and small series. Outcome vary according to severity and may range from double intrauterine fetal demise to two healthy neonates without major morbidity at birth, besides large inter-twin Hb differences. Severe anemia can be seen at birth in the donor, requiring blood transfusion, and severe polycythemia in the recipient, requiring partial exchange transfusion. Cases of severe cerebral injury in TAPS have also been described but outcome seems to be much better than in classic TTTS. In 19 pairs of twins affected by TAPS, matched to 38 pairs of non-affected twins, neonatal mortality and morbidity rates were similar to controls [168].

Twin Reversed Arterial Perfusion (TRAP) Syndrome

This is a very severe form of TTTS complication occurring with monochorionic placentation, due to unidirectional arterio-arterial placental anastomosis. It can be diagnosed in the first trimester [169]. It affects about 1 % of MC twins,

with a prevalence is 1:35,000 births. There are two theories to explain the phenomenon, both resulting in artery-to-artery anastomosis between the umbilical arteries of both twins. One theory states that the primary event is a teratological accident with severe abnormal development of the fetal heart, resulting in absence of the structure (hence "acardiac"). The vascular anastomoses are felt to be secondary. According to the second explanation, the primary event is the development of anastomoses and reversed blood perfusion from the donor (pump) fetus to the acardiac (recipient) twin, as demonstrable by Doppler studies [170, 171] (Fig. 14.14). This is responsible for secondary fetal cardiac hypoplasia [172] and amorphic development of one twin

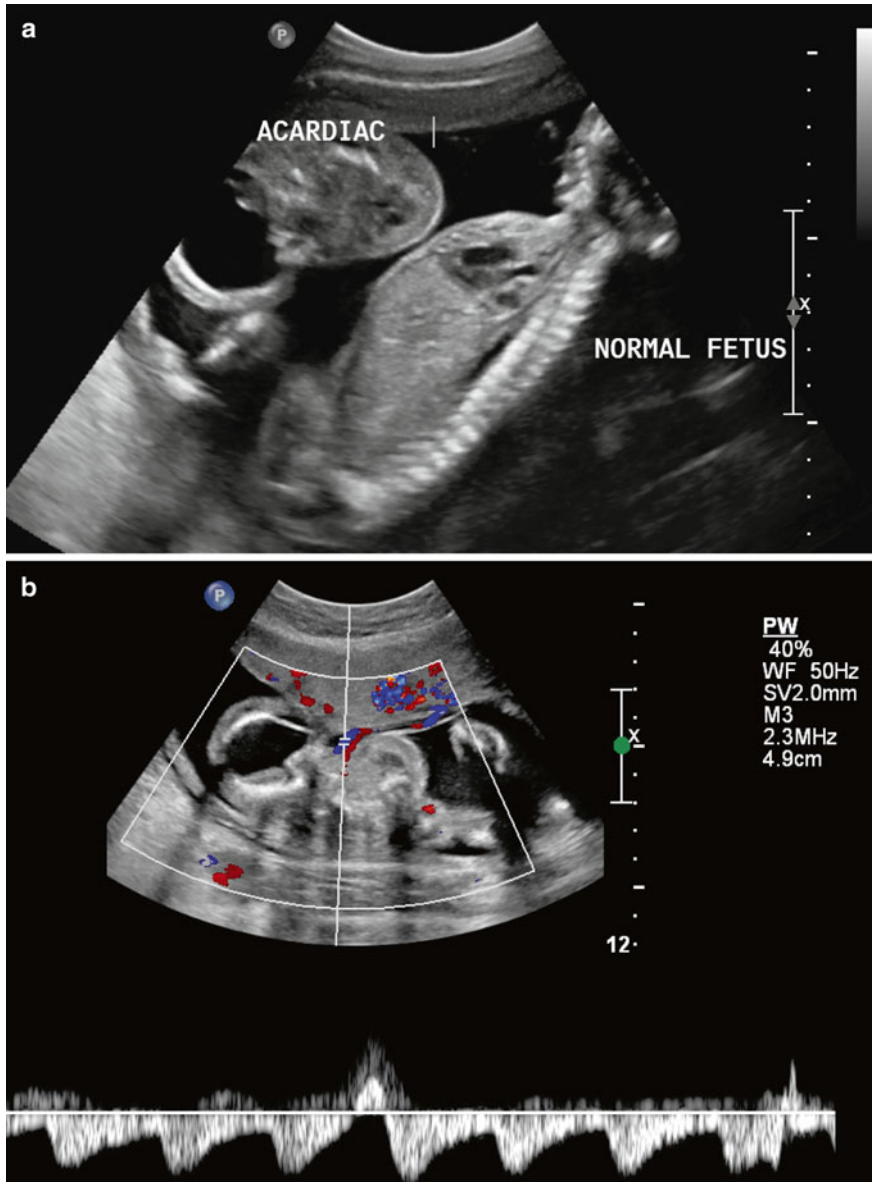

Fig. 14.14 TRAP sequence. (**a**) The acardiac twin is in the *upper part* of the image, as marked. Some vague anatomy can be recognized. (**b**) Doppler velocimetry demonstrates flow away from the transducer in the umbilical artery of the acardiac twin, i.e., reversed, from the placenta towards the fetal body

with poor formation of the head, trunk, and upper extremities but, occasionally recognizable spine and lower extremities. The reason for this differential development is that deoxygenated blood from the pump twin crosses the placenta through artery-artery anastomosis, resulting in retrograde flow to the acardiac fetus. The lower part of the body extracts the remainder of the oxygen, allowing for some development of the lower limbs, while the remainder of the body gets none. Acardiac twins often demonstrate a two-vessel cord and polyhydramnios. A somewhat older classification includes acardius amorphous, the least differentiated, appearing as a heterogenous mass, acardiac acephalus, the most common form of acardia, where the fetus lacks a head, thorax, and upper extremities (see Fig. 14.14), as well as acardius acornus and acardius anceps, the most developed form, with a head, thorax and abdominal organs but no heart. All acardiac twins may originate in the acardius anceps which evolves into the others because of poor oxygen supply to the remainder of the fetus. TRAP occurs in both MCMA and MCDA twin pregnancies. The overall pregnancy loss rate is estimated at 50 %, due to high output cardiac failure in the pump twin and preterm delivery [71]. Prognosis can be ascertained by calculating the ratio of the acardiac weight to pump twin estimated weight. The weight of the acardiac twin is calculated by the formula: weight (g) = 1.2 × (longest dimension (cm))^2 − 1.7 × longest dimension (cm) [173]. If the ratio is above 70 %, this indicates dire prognosis, as do signs of congestive heart failure (such as non-immune hydrops) in the pump twin. Various treatment modalities have been described: cord occlusion (by embolization, cord ligation, laser coagulation, bipolar diathermy, and monopolar diathermy and intrafetal ablation (by alcohol, monopolar diathermy, interstitial laser, and radiofrequency) with intrafetal ablation appearing to provide the best results [174].

Conjoined Twins

Twinning occurs in approximately one of every 87 live births. One-third of these are monozygotic twins and about 1 % of monozygotic twins are conjoined. Conjoined twins represent a rare entity with estimates ranging from 1 in 75,000 to 1 in 250,000 deliveries [22, 23]. In the USA, the incidence is 1 per 33,000–165,000 births and 1 per 200,000 live births [175]. Conjoined twins are MCMA with the diagnosis usually made in the second trimester, although early, first trimester diagnosis is also feasible [176, 177]. They are more common among females than males (3:1 in live born), and in nonwhites than whites [178]. For unclear reasons, it seems to be more common in Indian and African population. Stillbirth rate is very high (40–60 %). More cases are being reported now because of the routine use of ultrasound in early pregnancy [179–181]. Conjoined twins may be symmetrical with two well-developed bodies or asymmetrical where one is normally developed and the second is incomplete, for example twin reversed arterial perfusion or TRAP (previously called acardiac twin) or parasitic twin or fetus in fetu, a very rare condition where a monozygotic, MCDA abnormal twin with rudimentary anatomy is contained within a host twin [182].

Classification of conjoined twins is according to the site of union [183]. The most common types are the following:

1. Thoracoomphalopagus (joined at chest or abdomen or both), 75 % (Fig. 14.15). Thoracopagus generally share a heart (Fig. 14.16), which renders separation to save both twins virtually impossible.
2. Pyopagus (joined at the buttocks), 18 %.
3. Ischiopagus (joined at the ischium), 6 %.
4. Craniopagus (linked at the cranium), 2–5 %.

Management, outcomes, and postnatal issues are beyond the scope of this book [180, 184–186].

Cord Entanglement

This complication of MZ twins (designed as uniovular) was already described (not by ultrasound!) in 1952 [187]. It may begin early in the pregnancy, as soon as fetal (nonvoluntary) movements are initiated, around 7–8 weeks GA [188].

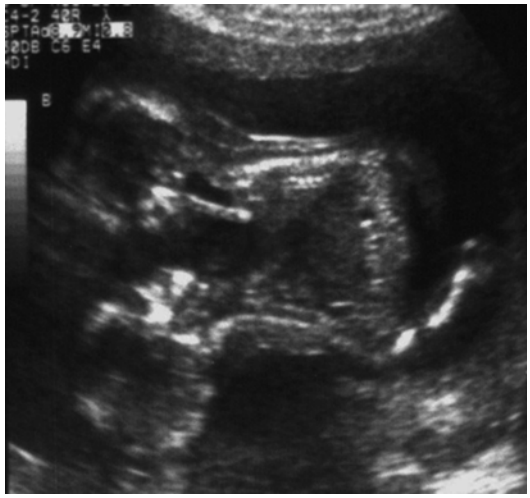

Fig. 14.15 Conjoined twins, 13 weeks. This is a typical thoraco-omphalopagus, the most common type, with joining at the thorax and abdomen levels

Major risks include intermittent cord compression which may result in neurological damage although a direct cause-effect relation is hard to prove [73] and complete occlusion with fetal demise [189]. Ultrasound is very useful to detect this condition specifically with the use of spectral and color Doppler. Color Doppler demonstrates a complex vascular mass [190, 191] (Fig. 14.17). Three-dimensional ultrasound can also be used to demonstrate the entanglement [192, 193]. There are several Doppler waveform characteristic of entanglement: persistent absent end-diastolic velocity in the umbilical artery [194] and pulsatile, high velocity waveform, with absent diastolic in the umbilical vein [195]. A notch in the umbilical artery before the entanglement region, indicating downstream elevated resistance was described as a specific sign associated with bad prognostic [196, 197], although more recent studies seem to indicate that the presence of an umbilical artery notch in cases of cord entanglement, without other signs of fetal deterioration, are not indicative of an adverse perinatal outcome [75].

The previously cited dire prognosis [189] may, in fact, be less dire than originally described [198]. In a study of 114 monoamniotic twin sets (228 fetuses) with documented cord entanglement at delivery, cord entanglement itself did not contribute to prenatal morbidity and mortality [199]. In another report, umbilical cord entanglement was present in all 18 sets of monoamniotic twins when it was systematically evaluated by ultrasound and color Doppler [73]. Perinatal mortality was mainly a consequence of conjoined twins, TRAP, discordant anomaly, and spontaneous miscarriage before 20 weeks' gestation.

Screening for Genetic and Morphologic Abnormalities[1]

Twins are at increased risk for genetic anomalies, as clearly documented in a study of 5.4 million births, from 14 European countries, of which 3 % were multiple [200]. The risk of karyotypic anomalies is different between monozygotic and dizygotic twins. For MZ twins, the age-related risk to simultaneously be abnormal is the same as in a singleton gestation, although, from a maternal standpoint, the risk to the pregnancy to have one affected fetus is twice the risk of a singleton in cases of twins, three times in the case of triplets, etc. For dizygotic twins, however, the risk of one being affected is similar to a singleton but the risk of both being affected is much lower. In fact it is the square of the risk of a singleton: for instance if the age related risk of the mother is 1:250, the risk of both twins, if dizygotic, to be affected is 1:250×1:250 or 1:62,500 [201]. Screening for trisomy 21 in multiple gestations is complicated [202, 203]. Local prevalence of aneuploidy in twins needs to be taken into account for all calculations of risk [204]. Serum screening alone is of limited value because a high value may indicate elevated risk but with no determination of which or how many fetuses are affected, since it is possible that an unaffected co-twin may "mask" the abnormal serum results of an affected one and the fact that for DZ or MZ twins the interpretation may need to be different [205–207]. Specific references may need to be utilized [208]. An acceptable screening test for aneuploidy in the first trimester twin pregnancy

[1] See also Chap. 8.

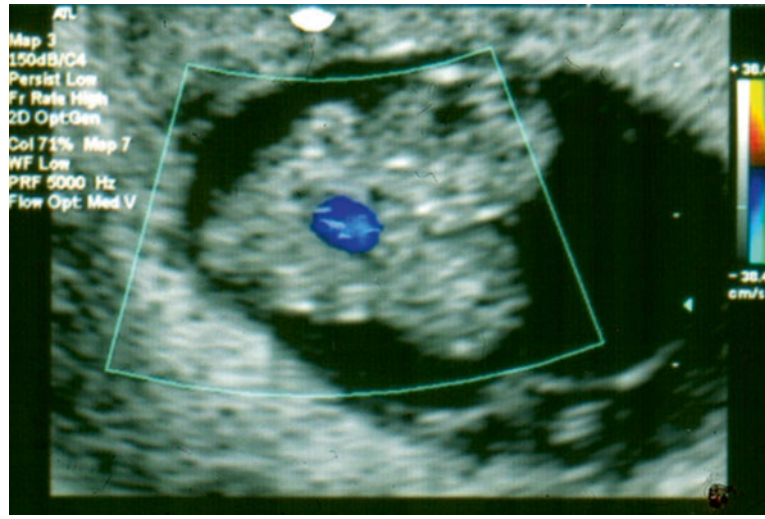

Fig. 14.16 Conjoined twins, 8 weeks. Color Doppler confirms conjoined twins with one heart

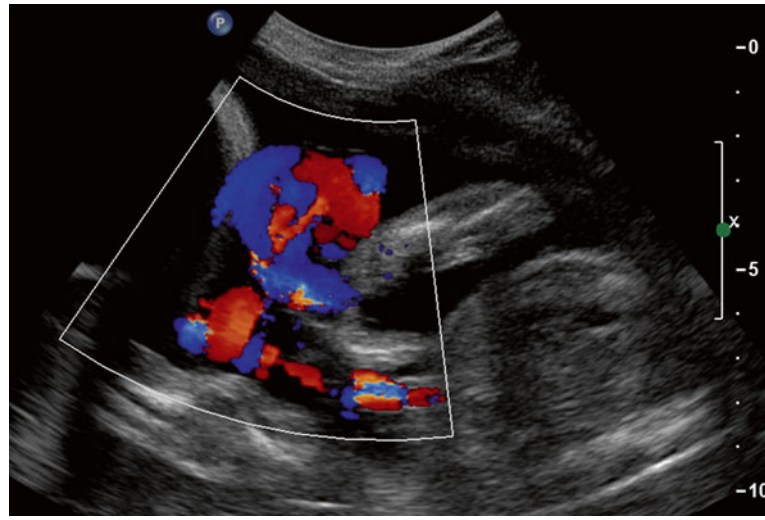

Fig. 14.17 Cord entanglement in monoamniotic twins. In this color Doppler image, a mass containing both cord is appreciated. The gestation is not in the first trimester but in the early second trimester

includes fetal nuchal translucency, combined with maternal age. Structural (as opposed to maternal serum) first trimester markers (including NT, nasal bone, tricuspid valve flow, and ductus venosus waveform) may be helpful in risk assessment for aneuploidy as they are independent measurements for each fetus, regardless of chorionicity [209]. Nuchal translucency (NT) screening is effective and is an excellent modality (when cell free fetal DNA is not available, see below) for twin pregnancies. When screening is done by nuchal translucency and maternal age, a pregnancy-specific risk should be calculated in MC twins. In DC twins, a fetus-specific risk is calculated [203]. Among twins, NT alone has a 69 % trisomy 21 detection rate [210]. Screening with first trimester serum analytes, combined with nuchal translucency (also known as First Screen) may also be considered. It decreases the false-positive rate. In a 2014 systematic review of first trimester combined risk assessment (nuchal translucency and maternal serum analytes) in twin pregnancies, test sensitivity in DC and MC twins was 86 % and 87 %, respectively [211]. Integrated screening with First Screen and second trimester serum screening is an option.

Naturally, in addition to trisomy 21, increased nuchal translucency is a marker for other aneuploidies, congenital malformations, and a sign of early development of TTTS [65, 161]. First-trimester combined NT and serum biochemistry has a 72 % DS detection rate, and an integrated screen will have an 80 % DS detection rate at a 5 % FPR [210]. The issue of "vanishing twin" (see below) is specifically problematic since early loss of one or more embryos of a multiple gestation may affect analyte levels [212]. In known cases, NT screening may be the preferred option. When screening is done by nuchal translucency and maternal age, a pregnancy-specific risk should be calculated in MC twins. In DC twins, a fetus-specific risk is calculated [203]. Some laboratories that perform noninvasive DNA screening (NIDS) with MPS methodology offer testing for twin gestations after it has been validated for twins. Testing for monozygotic twins is expected to perform similarly to a singleton gestation, although testing in dizygotic twin and higher-order multiple gestations is complicated by the fact that the per-fetus fetal fraction may be lower [213]. In fact, the non-reportable rate is higher (7.4 %) than that for singleton pregnancies (2 %). Additionally, if one fetus is euploid while the other is aneuploid, there is a dilution of the cell free fetal DNA from the aneuploidy fetus resulting in decreased detection rates compared to singleton gestations. Based solely on NIDS results, it is impossible to determine which twin is abnormal. Therefore, invasive testing (CVS or amniocentesis) is required to distinguish which twin is affected. Several false-positive results have been reported with biological basis, such as confined placental mosaicism (CPM), maternal chromosome abnormality and vanishing twin. Additional unexpected information such as undiagnosed molar pregnancy or vanishing twin may be detected by some NIDS methods [214].

The incidence of congenital anomalies is much higher in MZ twins, in fact three to five times higher than in DZ twins [215, 216]. Although this has been party correlated with assisted reproductive technologies [217], there seems to also be a direct relation with the twinning phenomenon itself, whether spontaneous or induced with a common etiology for both the MZ twinning and the early sequence of the malformation [218]. Most common structural anomalies in twins include anencephaly, facial clefts, holoprosencephaly, VATER association (vertebral defects, imperforate anus, esophageal fistula with tracheoesophageal fistula, radial and renal dysplasia), exstrophy of the cloaca malformation sequence, and sacrococcygeal teratoma, all of which should be recognized early by detailed ultrasound anatomy scan. In a large study by Glinianaia and colleagues 2329 twin pregnancies (4658 twins) and 147,655 singletons were compared. The rate of congenital anomalies in twins was 405.8 per 10,000 twins versus 238.2 per 10,000 singletons (rate ratios [RR] = 1.7, 95 % confidence interval [CI] 1.5-2.0]. In twins with known chorionicity (84.8 % of all twins), the prevalence of congenital anomalies in MC twins (633.6 per 10,000) was nearly twice that in DC (343.7 per 10,000; RR = 1.8, 95 % CI 1.3-2.5). There was an increased rate of congenital anomalies for all major types of anomalies in twin compared with singleton pregnancies, except chromosomal abnormalities [215]. Monozygo city specifically MCDA twinning, seems to be an independent factor for an increase in congenital heart disease (CHD) with a 9.18 relative risk increase in one report of 40 fetuses with CHDs among 830 fetuses from MCDA twin gestations [219]. Congenital heart disease, however, is also more common in DZ twins than in singleton [220]. Thus fetal echocardiography is, in fact, indicated in all wins. In a study of 844 pairs of twins, the prevalence of major congenital malformations was 2.7 % for MZ twins, 1.0 % for DZ twins, and 0.6 % for singletons. The concordance rate of major congenital malformations was 18 % for MZ twins, but no DZ pair was concordant for any major congenital malformation [221].

Are monozygotic twins "really" identical? They are very similar but genetically, most often, not "exactly" the same [222–224]. In fact, hundreds (360 by one estimate) of genetic differences may occur very early in fetal life. These may be due to post-fertilization events, such as chromosomal mosaicism, skewed X-inactivation, imprinting mechanisms, as well as DNA point

mutations or copy errors, taking place early after blastocyst splitting [224]. There are also, genetic differences due to mutations which may occur later in life as well as epigenetic[2] modifications, due to environmental factors [225, 226]. Another phenomenon explaining a difference in the karyotype of two MCMA twins is heterokaryotypia: a discordance in karyotype due to either an early postzygotic chromosomal rescue in one fetus or a mitotic error that leads to one trisomic fetus with a normal co-twin [227]. Discordance for a congenital anomaly is extremely problematic, from a moral, ethic, religious, philosophical, and, often, medical standpoints [228, 229]. Until intrauterine therapy is effective and safe (it may already be for a very small number of anomalies), the options include expectant management [230], termination of the entire pregnancy or selective feticide [231–233]. Selective termination of an anomalous DC twin is relatively safe with intravascular injection of potassium chloride or digoxin, although there is some increased risk of miscarriage or preterm delivery [234, 235]. In monochorionic twins, selective feticide needs to result in complete separation of the circulations [236, 237] and is, thus, best accomplished by sealing one umbilical cord with ligation [238], bipolar coagulation [239, 240], radiofrequency [241], or laser ablation [236].

Maternal Complications

As described in the introduction, maternal morbidity (and mortality) is increased in multiple pregnancies. Multiple pregnancy is the most powerful predictive factor for adverse maternal, obstetrical, and perinatal outcomes [242]. Pregnancy induces physiological stress to the maternal body and multiple gestations provide even additional strain and nutritional demands [243]. Most of the complications do not become clinically apparent in the first trimester but later in pregnancy, such as preeclampsia and diabetes [244]. Among women with 684 twin and 2946 singleton gestations enrolled in multicenter trials, rates for both gestational hypertension and preeclampsia were significantly higher among women with twin gestations than among those with singleton gestations. Furthermore, adverse neonatal outcomes were more frequent in women with twin pregnancies and hypertensive complications [16]. In a study of over 23,000 women, 553 of whom had twins, after adjusting for age, race/ethnicity, body mass index, maximal systolic and diastolic blood pressure, smoking and parity, multiple regression analysis showed that twin pregnancy was associated with an approximately twofold increase in the risk for developing gestational diabetes. The risk was highest among African-American and young women [245]. Thromboembolic disorders are major causes of morbidity and mortality in the pregnant patient. Contributing factors are increased blood coagulability [246], elevated BMI, maternal age above 35 and, specifically, multiple gestation with an incidence rate of 6.3/10,000 year in singletons versus 18.2/10,000 year among women with multiple pregnancies [247]. Other complications more common in women carrying multiple gestations, most likely secondary to increased levels of various hormones, in particular βHCG, include hyperemesis gravidarum [248]—although this is not universally accepted as a more frequent complication in multiple pregnancies [249]—iron deficiency anemia [250], intrahepatic cholestasis of pregnancy [251] and pruritic urticarial papules and plaques of pregnancy or PUPPP. This is the most common specific dermatosis of pregnancy, with an incidence is 1/160–1/300 pregnancies [252]. The majority of patients are nulliparous and PUPPP is 8- to 12-fold more common in women with multiple gestations, possibly due to increased hormones levels, as stated above, or increased abdominal distension [253]. An additional complication is acute fatty liver. This is a rare condition, usually of the third trimester, complicating approximately 1 in 10,000 singleton gestations [254] but, of all the published cases, 14 % have been reported in twin gestations [255]. The rate seems to be 7 % in triplet pregnancies [256].

[2] Epigenetics: level of activity of any particular gene (i.e. switched on, off, or partially switched on or off).

Higher Order Multiple Gestations

These pregnancies (triplets, quadruplets, etc.) are at extremely high risk of complications [257]. The classic teachings are that the prevalence for triplets is $1:90^2$ and $1:90^3$ for quadruplets. Numbers have greatly changed with the introduction of ART [258–260]. Classification is based on chorionicity and amnionicity [261] (Figs. 14.18 and 14.19). In a study of 49 consecutive sets of triplets, including 18 sets of spontaneously conceived triplet pregnancies and 31 sets resulting from ART the rate of MZ twin pairs was 48 % among spontaneously conceived triplet pregnancies; 30 % of DC triplet pregnancies were MZ and 70 % DZ; 20 % of trichorionic (TC) triplet pregnancies were DZ and 80 % trizygotic (TZ). For triplet pregnancies conceived using ART, the rate of MZ twin pairs was 6.5 %; 100 % of DC triplet pregnancies were DZ; 4 % of TC triplet pregnancies were DZ and 96 % TZ [261]. Early complications, such as genetic anomalies, growth discordancy, TTTS are similar to twin pregnancies, depending on placentation, although, naturally, much more challenging from a management standpoint [258, 262, 263]. Incidence of congenital anomalies is not increased, compared to twins [259]. The complications are mostly later in pregnancy. In a study of 316,696 twin, 12,193 triplet, and 778 quadruplet pregnancies, compared with mothers of twins, mothers of triplets and quadruplets were more likely to be diagnosed with preterm premature rupture of membranes (AORs, 1.53, 1.74, respectively), pregnancy-associated hypertension (AORs, 1.22, 1.27), and excessive bleeding (AORs, 1.50, 2.22), to be delivered by cesarean section (AORs, 6.55, 7.38) at <29 weeks of gestation (AORs, 3.76, 7.96),

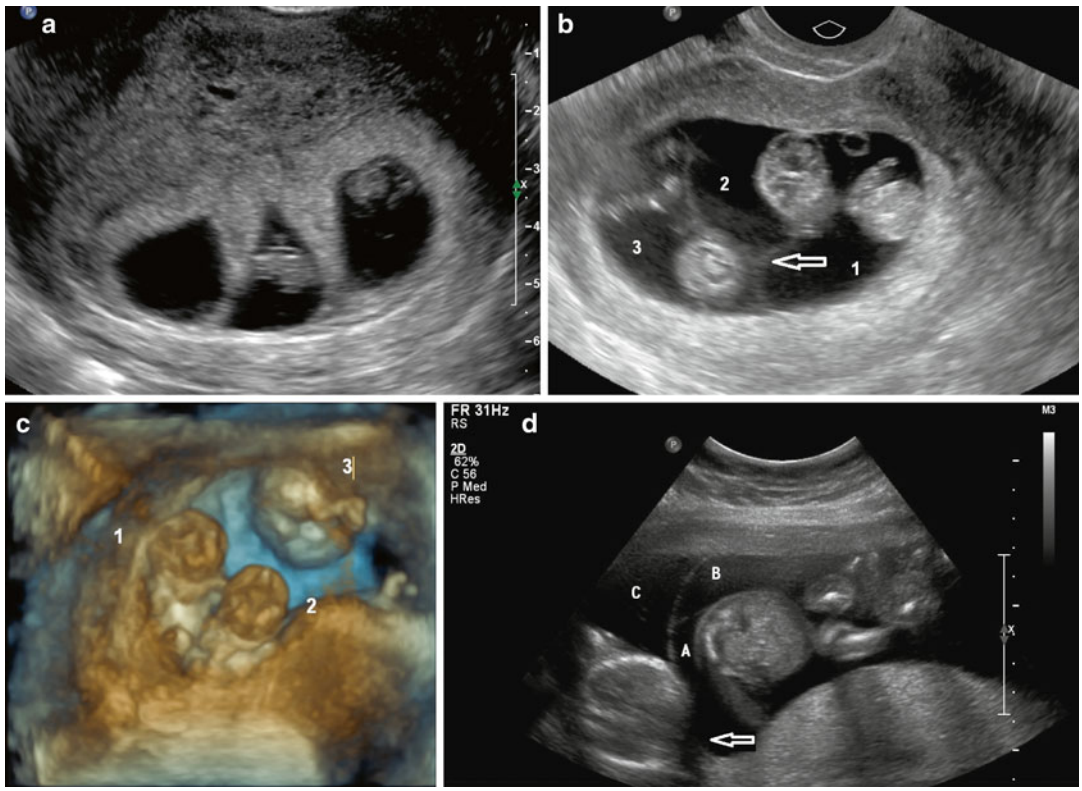

Fig. 14.18 Triplets. (**a**) Early first trimester trichorionic triplet pregnancy. (**b**) The ipsilon sign (*arrow*) allows diagnosis of trichorionic pregnancy. (**c**) 3D view of triplet pregnancy. Although two "lower" fetuses appear to be in one sac, the pregnancy is trichorionic, as demonstrated by the ipsilon sign. (**d**) Dichorionic triplets. Triplets A and B share a chorionic sac but are in separate amniotic sacs. Triplet C is in its own chorionic and amniotic sac. The *arrow* points to the twin peak sign. This confirms that triplet C is in its own chorionic and amniotic sac

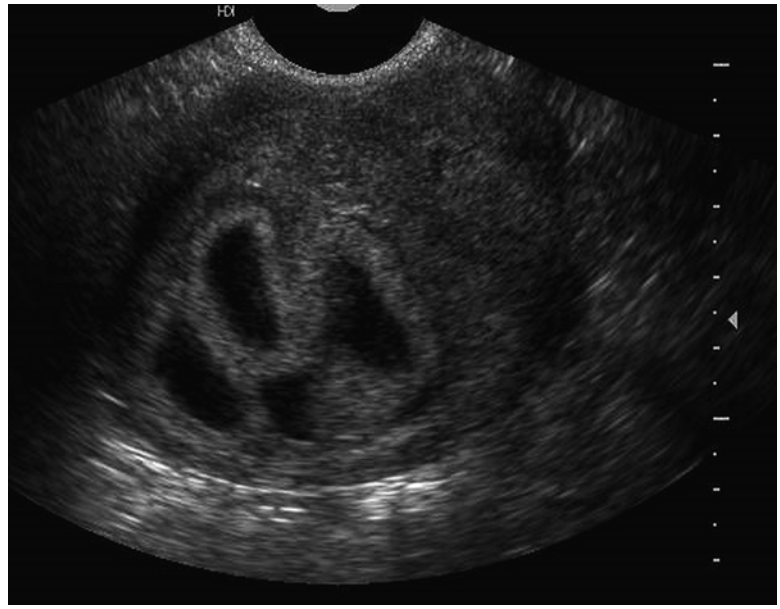

Fig. 14.19 Quadruplet pregnancy. Four distinct gestational sacs are demonstrated, with what appears to be thick separations between them. This represents quadrchorionic–quadramniotic placentation, in a patient who underwent ovulation induction

and to have one or more infants die (AORs, 3.02, 4.07). The rate of maternal complications is also increased compared to twin pregnancies where it is already increased compared to singletons. In a retrospective study of 57 triplet gestations, preterm labor occurred in 86.0 %, anemia in 58.1 %, preeclampsia in 33.3 %, preterm premature rupture of the membranes in 17.5 %, postpartum hemorrhage in 12.3 %, and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome in 10.5 % [264].

Invasive Diagnostic/Therapeutic Procedures in Twins

This is addressed in details in Chap. 20 of this book.

Teaching Points

- Multiple births comprise today 3 % of all live births in the USA.
- Dizygotic form 70 % of twin pregnancies and monozygotic, 30 %.
- Determination of placentation (chorionicity and amnionicity) should always be attempted when performing an ultrasound and should be reported.
- All twins are at increased risk for genetic anomalies.
- Vanishing twin, death of one fetus, discordant fetal growth, discordance for genetic/structural anomaly and partial mole are complications unique to twin pregnancies.
- Complications specific for monochorionic twins are TTTS and its variants and (TTTS, TAPS, TRAP) as well as conjoined twins and cord entanglement in monoamniotic twins.
- Maternal complications are common in women carrying multiple gestations, such as preeclampsia, gestational diabetes, thromboembolic disorders, cholestasis of pregnancy and acute fatty liver, as well as being exposed to a much higher risk of operative delivery.
- Classification of high order multiple gestations (triplets and above) are by placentation, similar to twin gestations.

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First-Trimester Ultrasound: Early Pregnancy Failure

15

Timothy P. Canavan and Joan M. Mastrobattista

Introduction

Ultrasound imaging introduced almost four decades ago opened up a visual window for pregnancy inspection. With the advent of higher-frequency intravaginal probes, sonologists were able to study the progression of first-trimester pregnancies in great detail. Markers of successful pregnancy as well as signs of pregnancy failure were defined. In this chapter, current medical evidence behind imaging and diagnosis of first-trimester pregnancy failure are reviewed. We emphasize that no single finding can substitute for clinical judgment when examining and interpreting available data. Most pregnancy failures present with more than a single sonographic or biochemical finding.

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Definitions

- *First-trimester pregnancy failure* (pregnancy failure): lack of sonographic evidence of present or expected viability
- *Threatened abortion*: vaginal bleeding in a viable pregnancy up to 20 weeks gestation in the presence of a long, closed cervix
- *Completed abortion*: complete passage of the embryo, amnion, and chorion
- "*Missed abortion*": is terminology not currently recommended since it does not adequately describe the pathophysiologic events [1]
- *Anembryonic pregnancy*: an abnormal pregnancy composed of a gestational sac without evidence of an embryo when one is expected
- *Embryonic demise*: presence of an embryo without cardiac activity when cardiac activity is expected

Risk Factors for Failure

Numerous risk factors are associated with first-trimester pregnancy loss; however, 40–50 % of losses are unexplained. Medical risk factors for pregnancy loss are listed in Table 15.1. Clinical

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Table 15.1 Medical risk factors for first-trimester pregnancy failure

Known etiologies	Possible etiologies
Parental chromosomal abnormality	Environmental exposures
Untreated hypothyroidism	Heritable and/or acquired thrombophilias
Uncontrolled diabetes mellitus	Infection
Septated congenital uterine anomaly	Maternal alcoholism
Asherman's syndrome	Polycystic ovarian syndrome
Antiphospholipid syndrome	

factors associated with an increased risk for pregnancy failure include: increased age at first menses, lower beta human chorionic gonadotropin (β-hCG) levels, lower progesterone levels, and vaginal bleeding [2–4]. Demographic characteristics that have been linked to pregnancy failure include advanced maternal age, cigarette smoking, and a history of pregnancy loss. Stern and associates prospectively followed 83 pregnancies from 4 to 12 weeks of gestation and found that women with at least two prior spontaneous abortions were almost four times more likely to have a pregnancy failure after documentation of cardiac activity at 6 weeks compared to subjects without a history of recurrent pregnancy loss [5].

Chemical Evidence of Pregnancy Failure

There is very little evidence to support biochemical screening for pregnancy viability. Studies evaluating pregnancy-associated plasma protein A (PAPP-A), estriol, α-fetoprotein, and inhibin A did not find statistical association with a change in these markers and early pregnancy loss. However, β-hCG and progesterone levels may have a direct relationship with early pregnancy maturation. Several studies have reported a mathematical relationship between rising β-hCG levels and "normal" pregnancy maturation. Kadar and associates reported that a 66 % rise in the β-hCG level in 48 h is associated with a normal intrauterine pregnancy [6]. However, significant weaknesses are noted in the study sample size and methodology rendering this conclusion unreliable. The study was based on only 20 patients who were sampled inconsistently at 1- to 5-day intervals, and the 48-h interval was determined after lowering the confidence interval to 85 %. A more recent study by Barnhart and associates found β-hCG increased by 24 % in 1 day and 53 % by 2 days; however, their sampling interval was also inconsistent, varying between 1 and 7 days, raising concerns about the reproducibility of their results [7]. Although the trend of a rising β-hCG titer may not reliably predict a viable pregnancy, a low β-hCG titer with an "empty" gestational sac should raise concern for pregnancy failure [8]. Low progesterone levels have also been associated with an increased risk for pregnancy failure [3, 9] This association increases significantly as progesterone levels fall below 30 nmol/L [3]. The association of pregnancy failure is strongest when correlating a woman's age and gestational sac size. Failure increases with advancing maternal age and increased sac size [3].

Multiple studies have attempted to determine a level of β-hCG at which a normal intrauterine pregnancy should be identified on ultrasound, frequently referred to as the discriminatory level. By transvaginal ultrasound (TVS), this discriminatory level was determined to be 1000 mIU/mL by some authors to 2000 mIU/mL by others [10]. This discriminatory level is defined as the threshold between an abnormal (spontaneous abortion or ectopic) and a normal intrauterine pregnancy. Doubilet and Benson reported the highest β-hCG that proceeded visualization of an intrauterine pregnancy by TVS and an eventual term live newborn as 4336 mIU/mL. They concluded that the β-hCG discriminatory level should not be used solely to determine first-trimester pregnancy management [10]. Therefore, a β-hCG discriminatory level is not a reliable marker for predicting pregnancy failure or an abnormal pregnancy.

Ultrasound Characteristics of Early Pregnancy

Events in early pregnancy follow a predictable sequence as documented by transvaginal sonography (see Chap. 7 for details). A gestational sac

is the first identifiable sonographic sign of pregnancy at approximately 5 weeks from the last menstrual period. The gestational sac is a small cystic structure, eccentrically located within the uterine cavity as a result of implantation within the endometrial lining. The sac is circular and well defined without any visible contents. By 5 weeks, 3 days, a yolk sac can be visualized as a round structure, usually eccentrically located. An embryo is first noted adjacent to the yolk sac around 6 weeks gestation. At this point, a fetal heart rate may be visualized. The embryo continues to increase in size and slowly takes on a more fetal form as it approaches 10 weeks of gestation with the crown-rump length increasing approximately 1 mm/day.

Imaging of the Early Pregnancy

The appearance and location of a first-trimester pregnancy are best imaged using a high-frequency transvaginal probe. With the transvaginal approach, the ultrasound probe is in close proximity to the pregnancy, allowing for excellent resolution. High-resolution imaging provides the necessary detail to visualize an early yolk sac, visualize and measure cardiac activity, and obtain an accurate crown-rump length measurement at an early gestational age. A transvaginal exam does not require a full bladder and in addition allows for an assessment of the adnexa and ovaries.

Ultrasound Evidence of Pregnancy Failure

Gestational Sac

The location and appearance of the gestational sac provide vital clues as to the likelihood of pregnancy failure. On initial sonographic evaluation, the location of the gestational sac is important to document and helps determine future viability and risk for pregnancy loss, as well as maternal morbidity, specifically from obstetrical hemorrhage if ectopic. The relationship of the sac to the cornual regions and to the cervix or prior uterine scar should be documented.

Location

Gestational sacs located in the extremes (cornua or cervix) of the uterine cavity will tend to be abnormal and either fail or need to be removed due to their risk for rupture and hemorrhage. Implantation in the cornual regions requires close observation with serial examinations. Those on the cavity side of the tubal ostia, referred to as subcornual, will tend to grow into the uterine cavity and proceed normally (Fig. 15.1a, b). Those within the interstitial portion of the tube will be cornual ectopic pregnancies and need additional therapy (Fig. 15.2). Implantations close to or in the endocervical canal tend to fail due to the poor vascular infrastructure; however, some will persist, becoming cervical ectopic

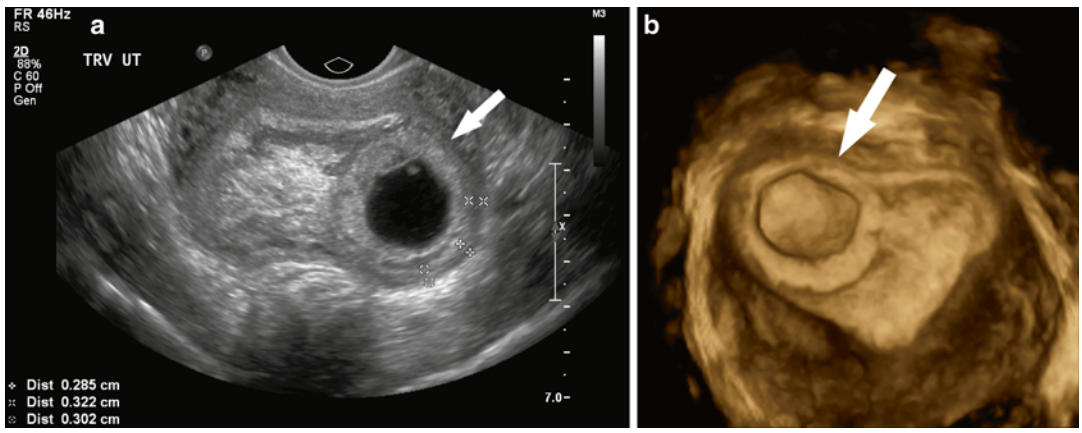

Fig. 15.1 (**a**) Subcorneal implantation. A transvaginal, axial, fundal image of a subcorneal implantation of a 5 week 0 day gestational sac is depicted. (**b**) Subcorneal implantation. In this 3D-rendered transverse image of the same pregnancy depicted in (**a**), the subcorneal implantation is identified by the *arrow*

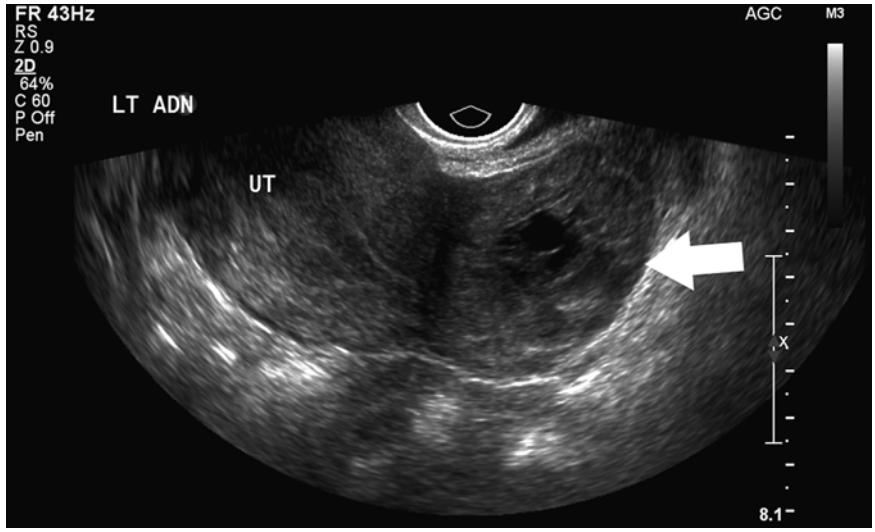

Fig. 15.2 Ectopic pregnancy. A corneal ectopic pregnancy (*arrow*) at 6 week 3 day is shown in this transverse image of the right uterine cornea

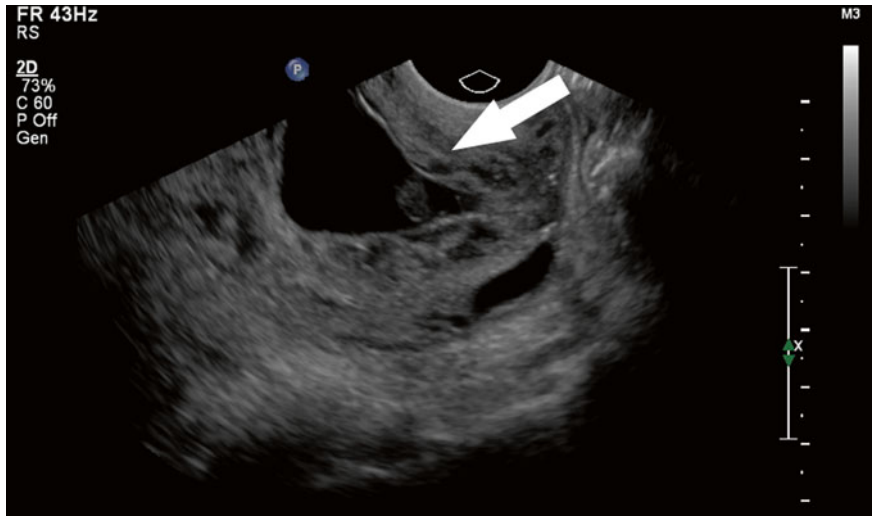

Fig. 15.3 Cervical ectopic pregnancy. A 7 week 6 day cervical ectopic pregnancy is depicted by the *arrow* in this midsagittal view of the cervix

pregnancies (Fig. 15.3). Cervical ectopic pregnancies will eventually rupture and/or hemorrhage risking significant maternal morbidity. Identification of the gestational sac low within the uterine cavity is associated with an increased risk for failure. Nyberg and coworkers assessed gestational sac location. They reported that when a gestational sac is located within the lower uterine segment, the risk for pregnancy failure is increased with a sensitivity and positive predictive value (PPV) of 20 and 94 % [11].

Appearance

The first sign of pregnancy identified by ultrasound is the gestational sac which is a round, anechoic cystic structure with an echogenic wall eccentrically located within the endometrial lining (Fig. 15.4a). The sac is usually identified when it reaches 2–3 mm in size in the fourth week of gestation. Gestational sac size is reported as a mean sac diameter (an average of the sagittal, transverse, and anteroposterior diameters of the sac). The appearance and size of the sac are

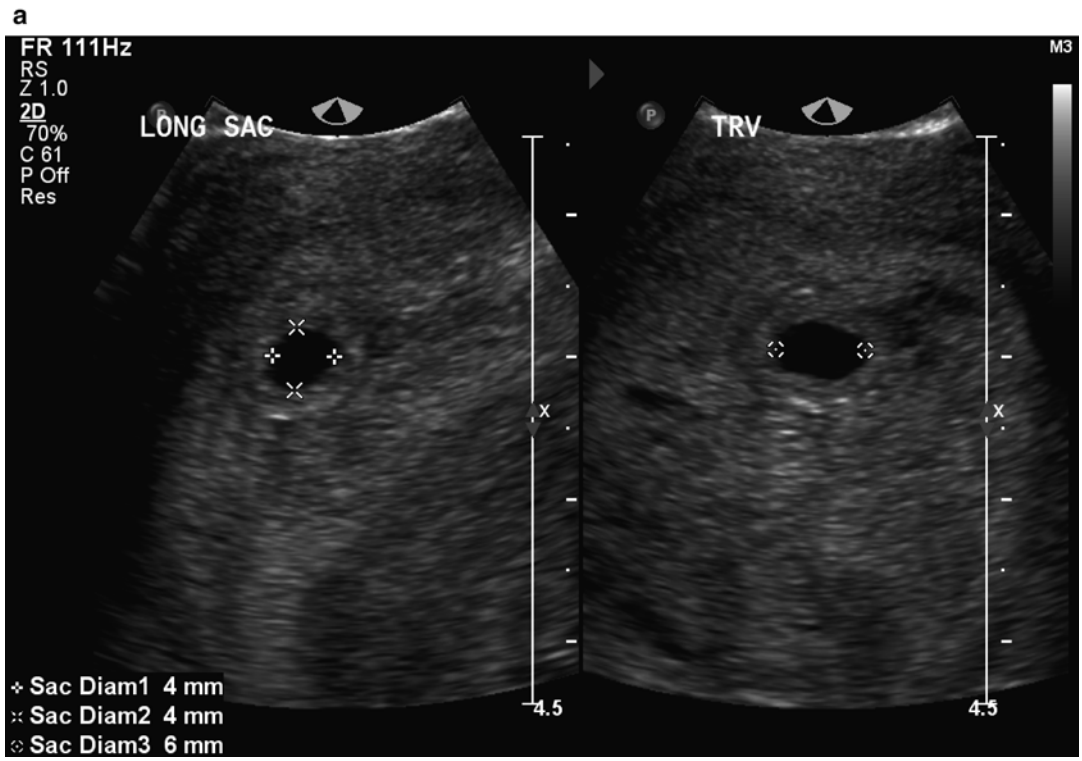

Fig. 15.4 Early gestational sacs. (**a**) A normal 4 week 1 day gestational sac is shown in the longitudinal and axial transvaginal images. Note the "donut"-shaped ring around the gestational sac known as a double decidual sac sign. (**b**) Transvaginal, midsagittal image of a pregnancy pseudosac within the uterine cavity is depicted with an ectopic pregnancy (not shown) at 5 weeks 2 days gestation. (**c**) Longitudinal and transverse images of an abnormal "tear drop"-shaped gestational sac with an abnormal-appearing yolk sac at 5 weeks 5 days gestation

important sonographic predictors of early pregnancy failure.

A centrally located cystic structure with a thin wall usually represents pseudogestational sac, a fluid collection within the uterine cavity, rather than a gestational sac (Fig. 15.4b). A pseudogestational sac can be seen when the pregnancy is located outside of the uterine cavity as with a tubal or cervical ectopic pregnancy. It tends to be "tear drop"-shaped and lacks the expected echogenic rim of a gestational sac and may contain debris. If a pseudogestational sac is suspected, further imaging is necessary to identify a possible ectopic pregnancy.

Although there is little research to predict outcome, gestational sacs that appear collapsed or contain a significant amount of debris are at high risk for pregnancy failure (Fig. 15.4c). These pregnancies may be anembryonic or may represent a recent embryonic demise. The debris may be the result of a recent hemorrhage. Careful examination of the sac for evidence of a yolk sac and/or embryo is required since the debris may mask these structures.

Nyberg and associates analyzed the appearance of the gestational sac in 168 subjects and found that a thin decidual reaction (≤2 mm), a weakly echogenic decidual reaction, and an irregular sac contour had a PPV for pregnancy failure of 96 %, 98 % and 97 %, respectively [11]. Moreover, the authors' report that a gestational sac located in the lower uterine segment has a PPV of 94 % for pregnancy failure (Fig. 15.5). A distorted gestational sac shape had the highest PPV for pregnancy failure at 100 %. Although the PPV was high, the sensitivity of these findings was low, ranging from 10 % for a distorted shape to 53 % for a weak echogenic decidual reaction (Fig. 15.6).

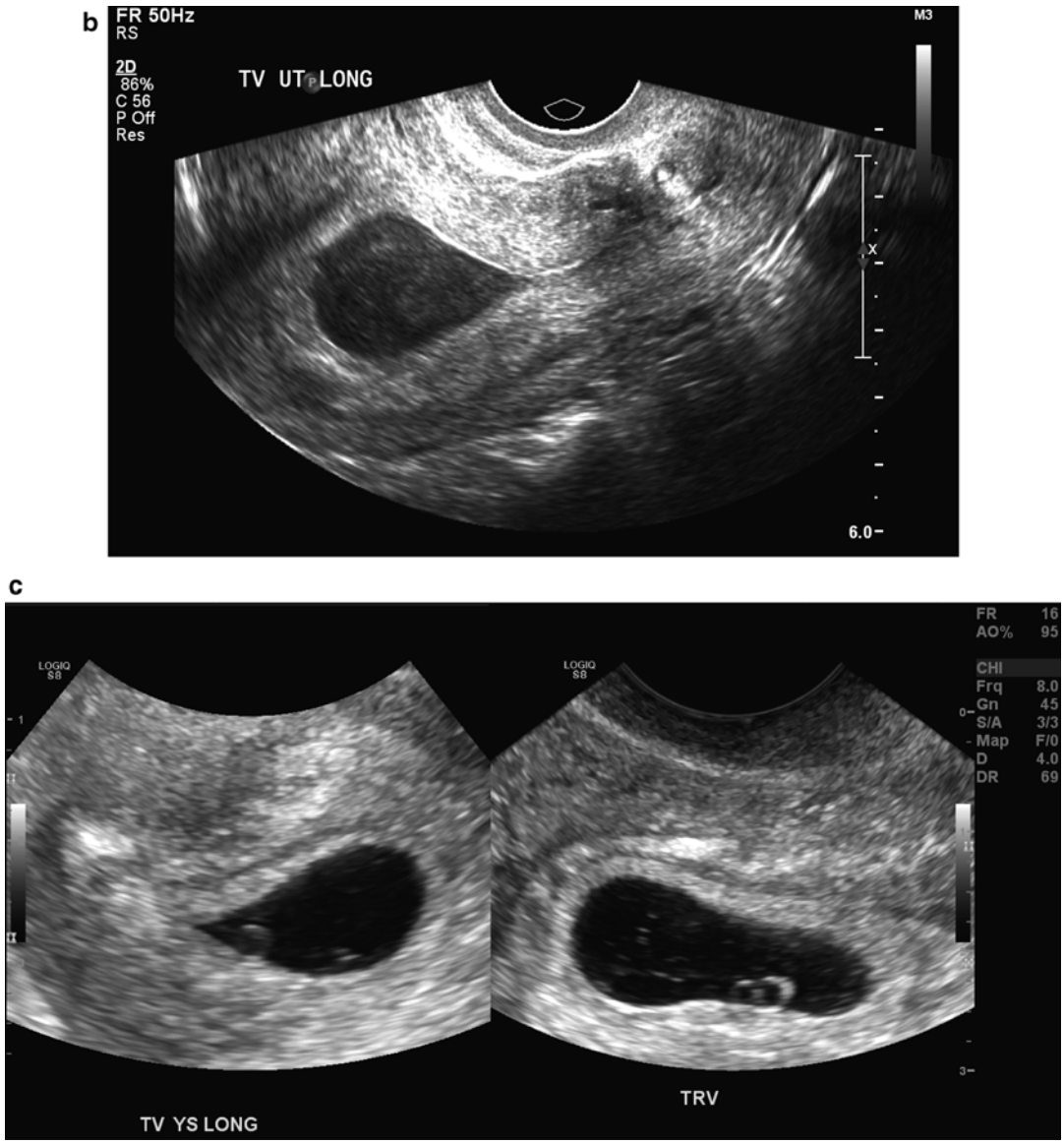

Fig. 15.4 (continued)

Several investigators have noted that the early gestational sac forms a cystic echogenic complex which expands into the uterine cavity and is outlined by the echogenic decidual tissue. This sonographic appearance has been referred to as the double decidual sac sign (DDS), and studies have advocated the absence of this sign as a predictor of pregnancy failure (see Fig. 15.4a). Nyberg and associates found that the absence of the DDS has a PPV of pregnancy failure of 94 %. Bradley and colleagues reported the utility of the DDS in differentiating an ectopic pregnancy from an early intrauterine pregnancy but found that the DDS was a poor predictor for pregnancy failure [11, 12]. Doubilet and Benson describe poor interobserver agreement for the presence of a DDS ($\kappa = 0.24$) and note that first-trimester outcome was unrelated to the presence of a DDS [13].

Yeh and associates described another early sonographic sign of pregnancy. They reported

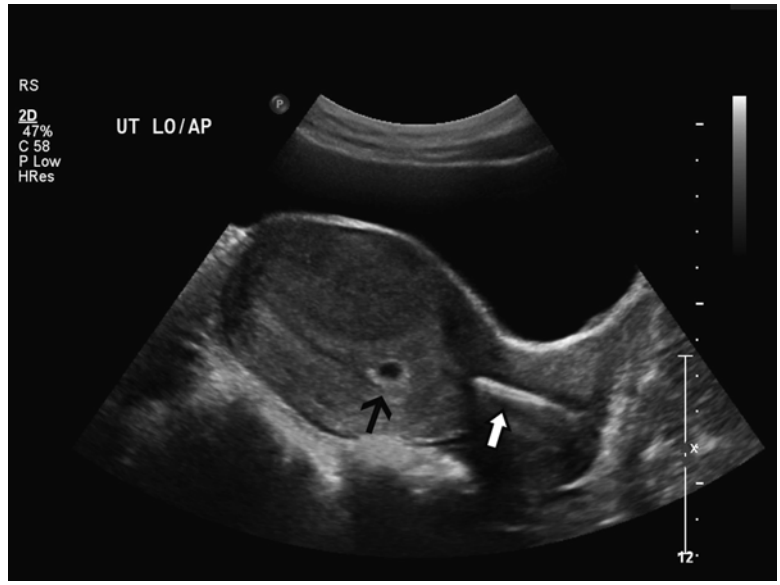

Fig. 15.5 Abnormally positioned gestational sac. This is a midsagittal, transabdominal image of a 5 week 0 day gestational sac implanted in the lower uterine segment portion (*solid black arrow*) of the uterine cavity with an intrauterine contraceptive device in the endocervical canal (*white arrow*)

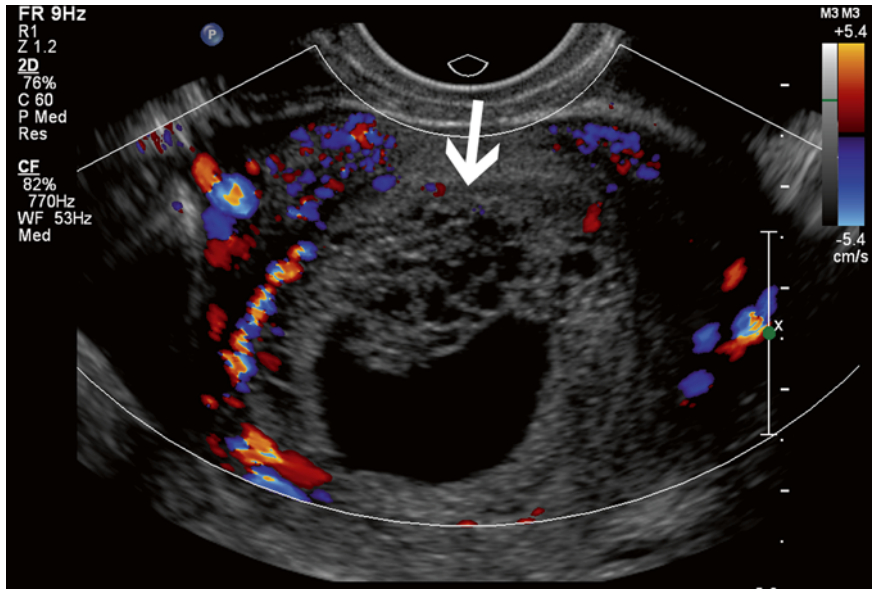

Fig. 15.6 Irregular gestational sac. A transvaginal, axial image is shown depicting an irregular 7 week 5 day gestational sac in a failed pregnancy found to be triploidy by karyotype. Note the cystic (hydropic) placenta (*arrow*) sometimes seen in triploidy

that the early gestational sac is implanted within thickened decidua on one side of the uterine cavity, and the combination of these sonographic findings was coined the intradecidual sign (IDS) [14] (Fig. 15.7). The IDS was identified in 92 % of intrauterine pregnancies as early as 25 days of gestation, yielding a sensitivity and specificity of 92 and 100 %. Laing and associates found the IDS to have a sensitivity and specificity of 34–66 % and 55–73 %, respectively, with poor interobserver agreement [15]. The overall accuracy for predicting an intrauterine pregnancy was only 45 %. Chaing and colleagues revisited the utility of an IDS for determination of an

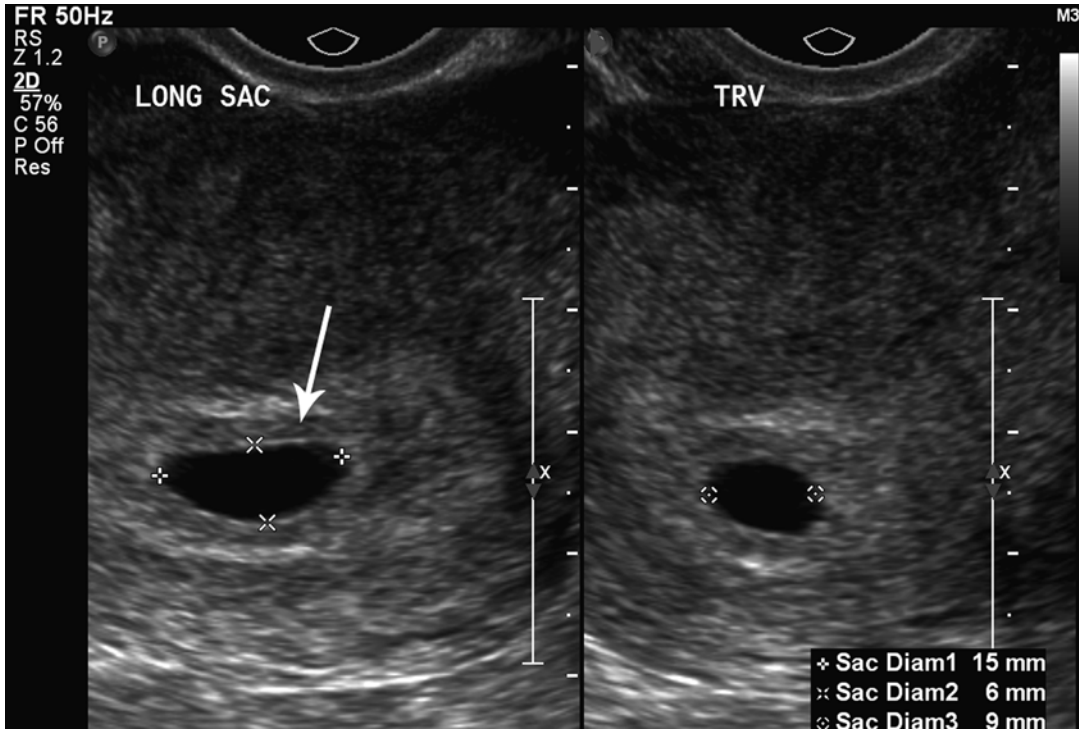

Fig. 15.7 Intradecidual sign. A transvaginal, axial image of a 5 week 1 day gestational sac with an intradecidual sign (*arrow*) is shown

intrauterine pregnancy and found more favorable sensitivity, specificity, accuracy, and interobserver agreement (kappa statistic) of 70 %, 100 %, 75 %, and 0.79, respectively [16]. Doubilet and Benson also investigated the IDS as a sign of a viable intrauterine pregnancy and found poor interobserver agreement with a kappa statistic of 0.23. They found no statistically significant relationship between the presence of an IDS and viability at the end of the first trimester [13]. Based on the present literature, the DDS and IDS are often not visualized or are difficult to discern, and the ultimate pregnancy outcome seems unrelated to the presence of these two findings. Given the poor agreement among investigators, these signs do not appear predictive of pregnancy success or failure.

Size/Growth

The most predictive criterion for identifying a failed pregnancy is the presence of a large gestational sac for expected age that does not contain an embryo. Several studies have investigated a critical value for the minimal mean sac diameter above which a normal embryo should reliably be identified by TVS. Initial studies suggested a cutoff of 16 mm but were based on small numbers [17]. Other studies identified empty gestational sacs with a mean sac diameter between 17 and 21 mm that subsequently were found to be viable pregnancies [18, 19]. Pexsters and associates found the interobserver error in the measurement of the mean sac diameter to be ±19 % [20]. Considering the results of these studies, a 21-mm mean sac diameter by one observer could be as high as 25 mm as measured by a second observer. Therefore, a mean gestational sac diameter of 25 mm, in the absence of an embryo, would be the best diagnostic cutoff for a failed pregnancy (Fig. 15.8).

A normal gestational sac grows approximately 1 mm per day during the first trimester (Fig. 15.9) [21]. However, predicting pregnancy failure by subnormal sac growth is not reliable [22]. Usual

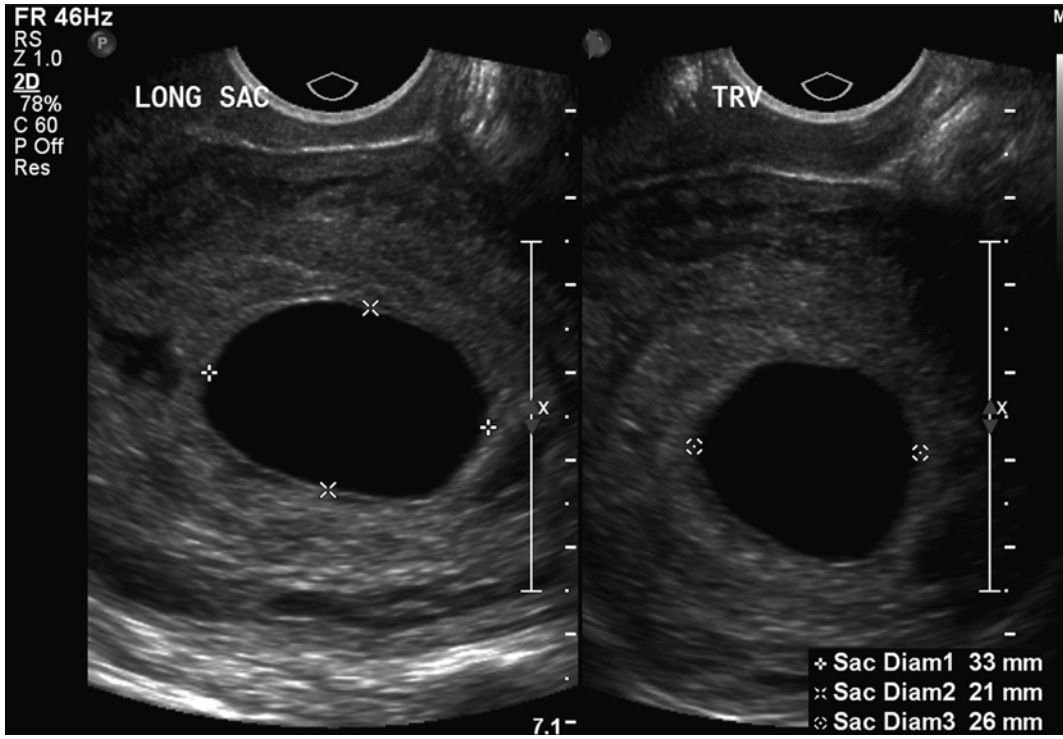

Fig. 15.8 Large, empty gestational sac. This is a transvaginal, axial image of an empty 7 week 5 day gestational sac with a mean sac diameter of 27 mm, indicating a failed pregnancy

Fig. 15.9 Graph depicts the mean gestational sac diameter in mm ± 2 standard deviations compared to the gestational age in weeks created with data from ref. [24]

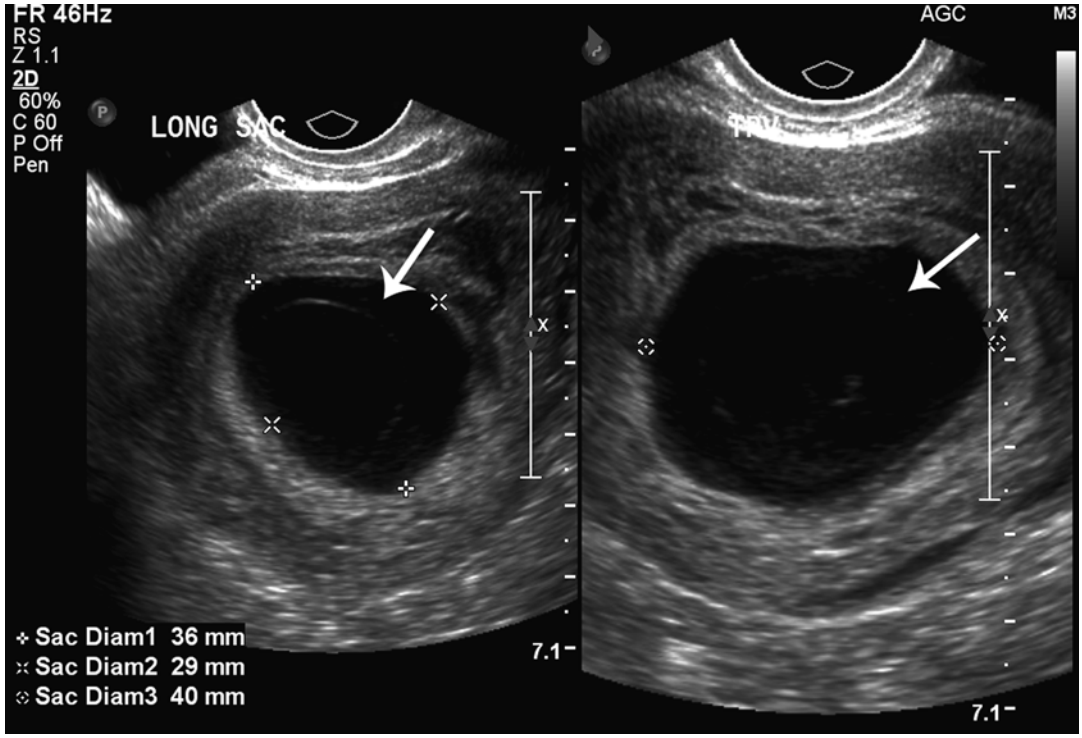

Fig. 15.10 Empty amnion. An empty amnion at 6 weeks 6 days gestation is shown (*arrows*) in this transvaginal, axial view of the uterus

timing of early pregnancy events (±0.5 weeks) includes visualization of the gestational sac by 4.5 weeks, yolk sac by 5.5 weeks and an embryo with cardiac activity by 6 weeks, but variation exists. A single examination at 6 weeks that does not demonstrate an embryo with cardiac activity is not diagnostic of pregnancy failure especially if the pregnancy is dated by the menstrual cycle, which is frequently unreliable. A second examination is recommended to confirm pregnancy failure. Once a gestational sac is visualized within the uterus, an embryo with cardiac activity should be identified sonographically within 14 days. If a gestational sac and yolk sac are visualized, an embryo with cardiac activity should be seen within 11 days [23, 24]. Failure to meet these milestones would be suggestive of pregnancy failure.

Amnion

The amniotic cavity is a space between the cytotrophoblast and the embryonic disc, which is lined by amnion cells. The amnion is usually visualized near the same time as the embryo (approximately 6.5 weeks). During the early first trimester (6.5–10 weeks), the diameter of the amniotic cavity is approximately equal to the embryonic crown-rump length (amniotic diameter = 1.1 × CRL − 0.07) [25]. A small or non-visualized embryo in a well-formed amniotic cavity is suggestive of a failed pregnancy. Horrow found that a CRL/amniotic cavity difference greater than 0.48 cm (0.86 ± 0.38 cm) was associated with pregnancy failure. McKenna and associates reported that an "empty amnion" (defined as a visible amnion without an embryo)

was always associated with pregnancy failure (Fig. 15.10) [26]. Yegul and colleagues described that a visible amnion with an identifiable embryo (less than 5.4 mm) without cardiac activity was associated with pregnancy failure. This finding was referred to as the "expanded amnion sign," and in their analysis, this sign had a PPV of 100 % [27]. A further study by this group found that visualization of an amniotic cavity without evidence of an embryo (referred to as the "empty amnion sign"), confirmed pregnancy failure regardless of the gestational sac size with a PPV of 100 % [28].

Placenta/Chorionic Frondosum

The chorion is formed from mesoderm and trophoblasts and becomes the wall of the chorionic cavity. The chorionic cavity is the anechoic fluid collection in which the embryo, amnion and yolk sac are suspended and grow, and is measured as the "gestational sac." The cavity is eventually obliterated by the expanding amnion, resulting in the single amniotic cavity.

The most significant concern for the chorion is hematoma formation. Bleeding during the first trimester of pregnancy is one of the most common obstetrical complications, occurring in approximately 14 % of all pregnancies [29]. This bleeding can result in hematoma formation of the subchorion. Multiple studies have linked subchorionic hematomas (SCH) with both early and late adverse pregnancy outcomes. The definition of a hematoma is not always clearly defined, but the majority of investigators recognize a hematoma as a crescent-shaped, hypoechoic fluid collection behind the fetal membranes and/or the placenta. Hematomas may be subchorionic (between the chorion and myometrium) or retroplacental (behind the placenta) and frequently become filled with debris as they age [30, 31] (Fig. 15.11a, b).

Vaginal Bleeding

Falco and associates followed 270 pregnant women with vaginal bleeding between 5 and 12 weeks gestation and found that 17 % developed SCHs. Pregnancy failure ranged from 6 to 84 %, depending on the presence of other factors such as the gestational sac CRL difference, menstrual sonographic age difference and the embryonic heart rate [2]. They found that the fetal heart rate was the most powerful predictor of pregnancy outcome in their linear regression model, with a low heart rate (less than 1.2 SDs which is 94 beats per minute (bpm) at 6 weeks gestation to 124 bpm at 10 weeks gestation) increasing the risk for pregnancy failure. Borlum et al. followed 380 women with vaginal bleeding and found an 11.3 % increased pregnancy loss rate in the presence of a SCH [32]. Schauberger and colleagues found that 14 % of women with a confirmed viable pregnancy by ultrasound performed for vaginal bleeding experienced pregnancy failure by 20 weeks gestation [33]. Additional studies on women with first-trimester vaginal bleeding have reported similar results of both early pregnancy failure and pregnancy loss up to 20 weeks gestation [34].

Hematoma

Multiple studies have investigated the risk of pregnancy loss after the identification of a SCH and the findings are mixed. Additionally, there is crossover between women with first-trimester vaginal bleeding and those in which hematoma formation is actually confirmed by ultrasound. Comparison of these studies is limited by the varied methodologies and study design limitations (small sample size, lack of a control group, limited description and analysis of patient characteristics and publication bias) [35, 36]. The rate of SCH ranged from 0.5 to 20 % in these studies, and while studies by Pedersen et al. and Stabile et al. found no association of SCH to pregnancy failure, other studies by Borlum et al. and Maso et al. found at least a twofold increased risk [32, 34, 37, 38]. Most studies did not find any statistical relationship between the hematoma volume and adverse outcome; however, Maso et al. found that the overall risk for spontaneous abortion was 2.4 times higher when the hematoma was identified before 9 weeks of gestation [34]. One of the largest studies by Ball and coworkers evaluated 238 subjects with a SCH and found a 2.8-fold

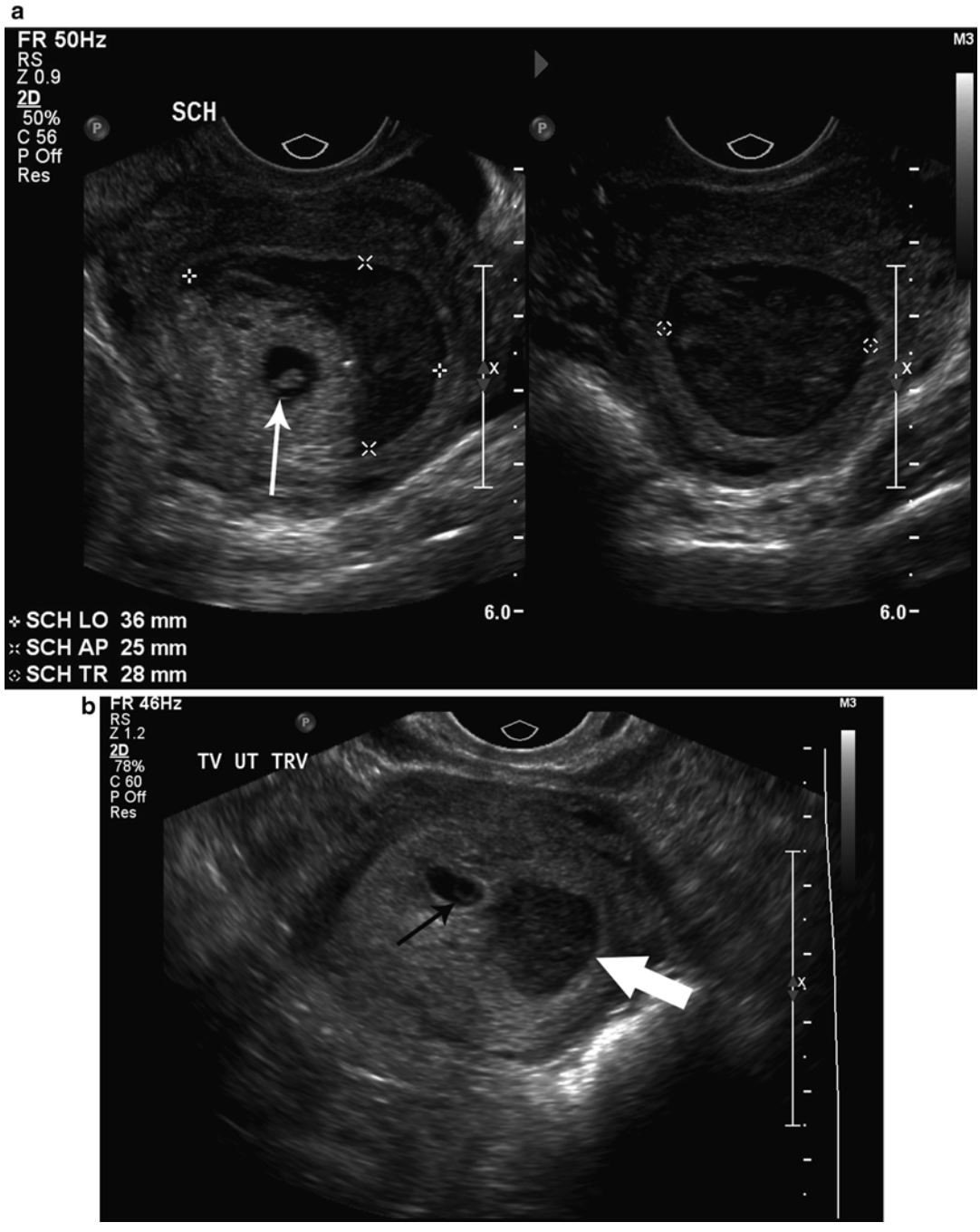

Fig. 15.11 (**a**) Subchorionic hematoma. A large subchorionic hematoma is denoted by calipers in this transvaginal, axial image at 5 weeks 5 days gestation, showing an early embryonic pole (*arrow*). (**b**) Subchorionic hematoma. This transvaginal, axial image shows a subchorionic hematoma (*thick white arrow*) in a 5 week 0 day gestation with a normal-appearing yolk sac (*thin black arrow*)

increased risk of spontaneous abortion (a loss before 20 weeks gestation) [31]. In those subjects with a SCH, vaginal bleeding increased the risk of spontaneous abortion compared to subjects without vaginal bleeding but findings did not reach statistical significance ($p = 0.057$) [31]. A systematic review and meta-analysis by Tuuli and coworkers calculated a 2.2-fold increased risk of spontaneous abortion in the presence of a SCH [35]. Based on these findings, it is reasonable to assume that a SCH is associated with a twofold increased risk for pregnancy failure.

Chorionic Bump

Harris and colleagues studied the association of a round avascular mass extending from the chorio-decidual surface into the gestational sac described as a chorionic bump, with first-trimester pregnancy outcome [39] (Fig. 15.12a, b). They hypothesized that chorionic bumps represent choriodecidual hemorrhages and reported that the chorionic bump was associated with a four-fold increased risk for pregnancy loss, mostly in the first trimester. Sana et al. performed a retrospective case-controlled trial and found that a chorionic bump identified in the first trimester had approximately double the risk of pregnancy loss compared to matched controls. Neither study found a statistically significant relationship between the size or location of the chorionic bump and the risk of pregnancy loss [40].

Vascular Pattern

Once a gestational sac is visualized, uteroplacental circulation can be identified in most viable pregnancies (Fig. 15.13). Moving echoes within the 8- to 11-week placenta detected by grey scale imaging is noted more frequently in those with pregnancy failure compared to viable pregnancies (88–100 % vs. 36–60 %, $p < 0.01$–0.001) [41]. In women with pregnancy failure, the placenta tends to have a mottled appearance due to numerous centrally located venous lakes (Fig. 15.14). Wherry and colleagues found that low-resistance arterial endometrial blood flow is associated with trophoblastic tissue but could not discriminate between a viable pregnancy and pregnancy failure [42]. Jaffe et al. prospectively followed color Doppler interrogation of the decidual spiral arteries and the intervillous space in 100 women at 7–12 weeks gestation and recorded pregnancy outcomes [43]. Thirteen women had pregnancy failure in the first trimester and six had second trimester medical complications including hypertension, preeclampsia and diabetes. Abnormal color Doppler imaging was defined as active blood flow in the intervillous space and a resistive index > 0.55 in the spiral arteries. A reassessment of their data targeting first-trimester failure yielded a sensitivity, specificity, PPV, and negative predictive value of 92 %, 82 %, 43 %, and 99 %, respectively. These findings suggest that color Doppler may be helpful in predicting pregnancy failure but should not be used alone as diagnostic.

Yolk Sac

The primary yolk sac regresses by week 2 or 3 of pregnancy and is no longer visible by ultrasound. The secondary yolk sac (YS) is the earliest embryonic landmark visualized by ultrasound; it is usually identified by about the 5.5 weeks when the gestational sac is about 8–10 mm (Fig. 15.15). However, in occasional normal pregnancies, the YS may not be visualized until a gestational sac size of 20 mm [19]. The yolk sac is a circular structure with a hyperechoic wall and measures approximately 3–5 mm. It increases in size steadily up to 8–11 weeks gestation and disappears by 12 weeks (Fig. 15.16). Identification of the YS confirms that an intrauterine fluid collection is a gestational sac even before the appearance of the embryo. Since the YS is continuous with the embryo, amnion, and connecting stalk in the early first trimester, it will typically be found close to the wall of the gestational sac.

Appearance

The description of an abnormal or deformed YS varies slightly by study, but the majority of investigators describe an abnormal YS as having any of the following: an irregular (non-circular) shape, wrinkled margins, indented walls, collapsed walls, thick echogenic walls, doubled

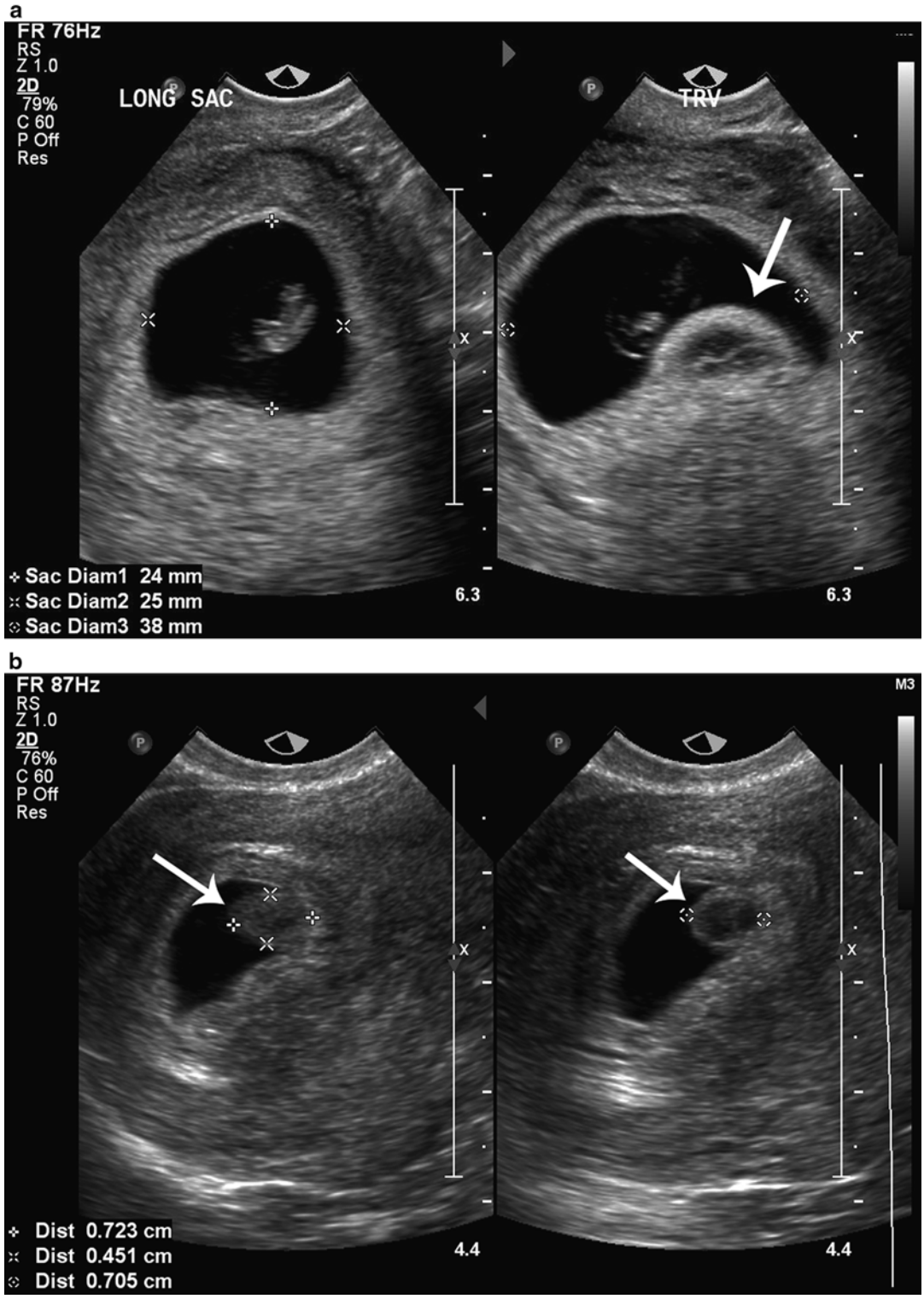

Fig. 15.12 (**a**) Chorionic bump. A chorionic bump (*arrow*) is visualized in the right longitudinal image of this 8 week 0 day gestational sac with an embryonic pole. (**b**) Chorionic bump. A chorionic bump (*arrows*) is measured in these transvaginal, axial and longitudinal images of a 5 week 0 day gestational sac

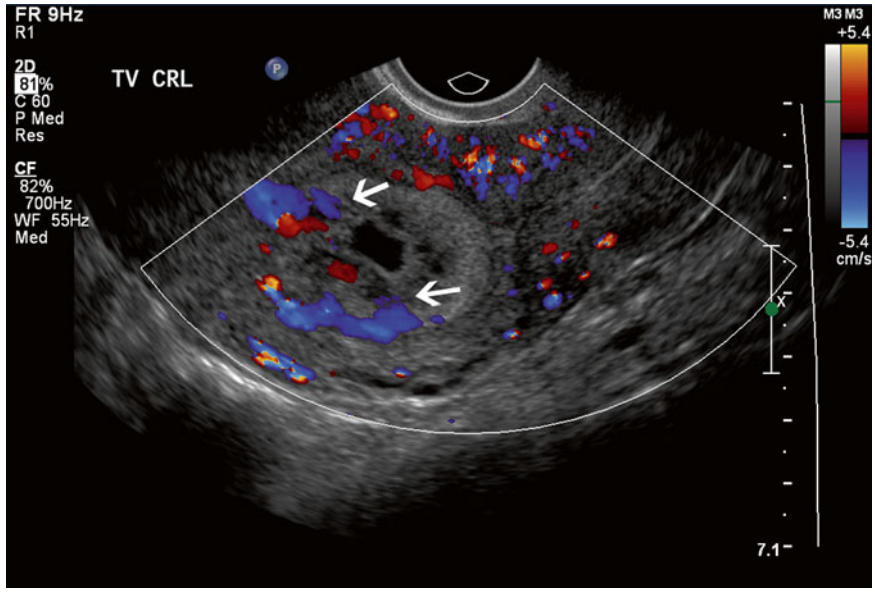

Fig. 15.13 Intervillous vascular flow. Color Doppler highlights the intervillous vascular flow (*arrow*) in this 5 week 6 day failed pregnancy

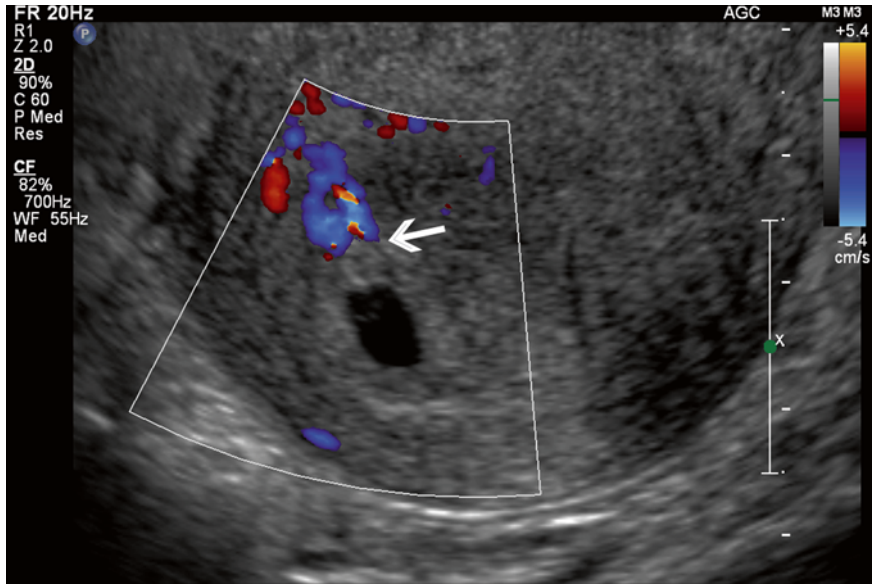

Fig. 15.14 Peritrophoblastic vascular flow. This image shows normal peritrophoblastic flow (*arrow*) in a 4 week 6 day pregnancy

(appearance of 2 or more YS) or containing echogenic spots or bands (see Figs. 15.4c, and 15.17a, b). An echogenic YS, with an echogenic central portion rather than anechoic has not been considered abnormal. Only one study described adverse outcomes in pregnancies with an echogenic YS, but several others report this finding in normal pregnancies [44]. Echogenic yolk sacs should be differentiated from a calcified YS in which acoustic shadowing is demonstrated. Calcified yolk sacs are usually indicative of a loss of fetal cardiac activity before 12 weeks of gestation [45].

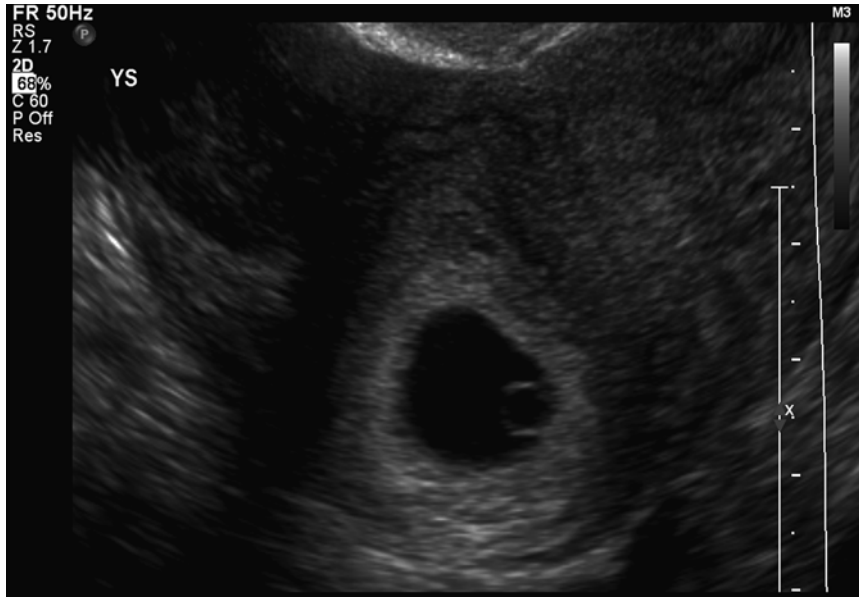

Fig. 15.15 Normal gestational sac and yolk sac. A normal 5 week 6 day gestational sac and yolk sac are shown in this parasagittal, transvaginal image

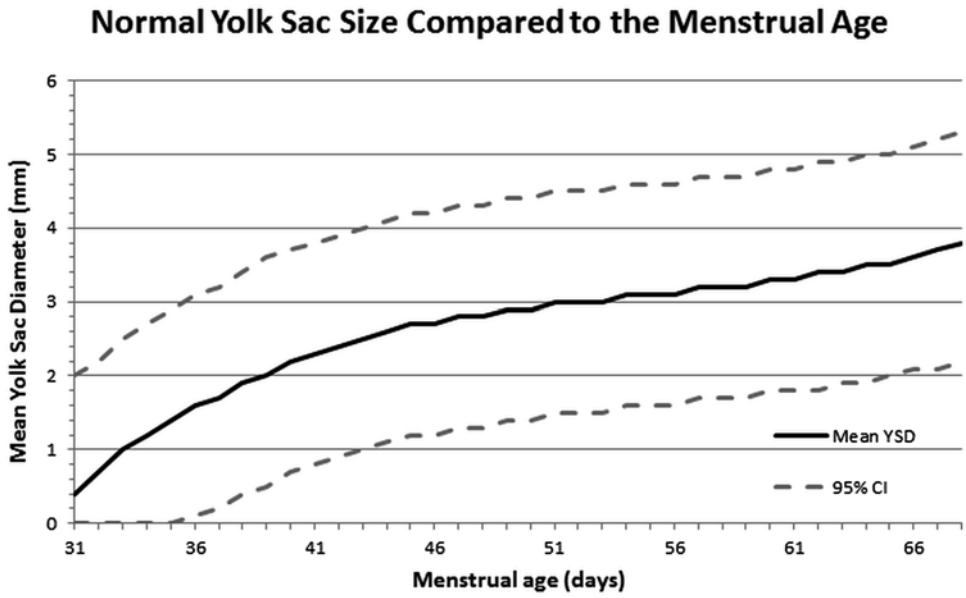

Fig. 15.16 Graph compares a normal yolk sac size in mm ± 2 standard deviations with the crown-rump length in mm using data from ref. [46]. Reprinted with permission from Lindsay DJ, Lovett IS, Lyons EA, et al. Yolk sac diameter and shape at endovaginal US: predictors of pregnancy outcome in the first trimester. *Radiology* 1992; 183: 115–118

Studies have been mixed on the risk of pregnancy loss associated with abnormal-appearing YS. Lindsay and Cho and their associates both found an increased risk of pregnancy loss with abnormal-appearing YSs, but both studies followed only a small number of affected pregnancies (7 and 5, respectively) [46, 47]. Kucuk et al. followed 19 women with an abnormal-appearing YS and found increased pregnancy loss with a sensitivity and PPV of 29 % and 47 % [48]. More

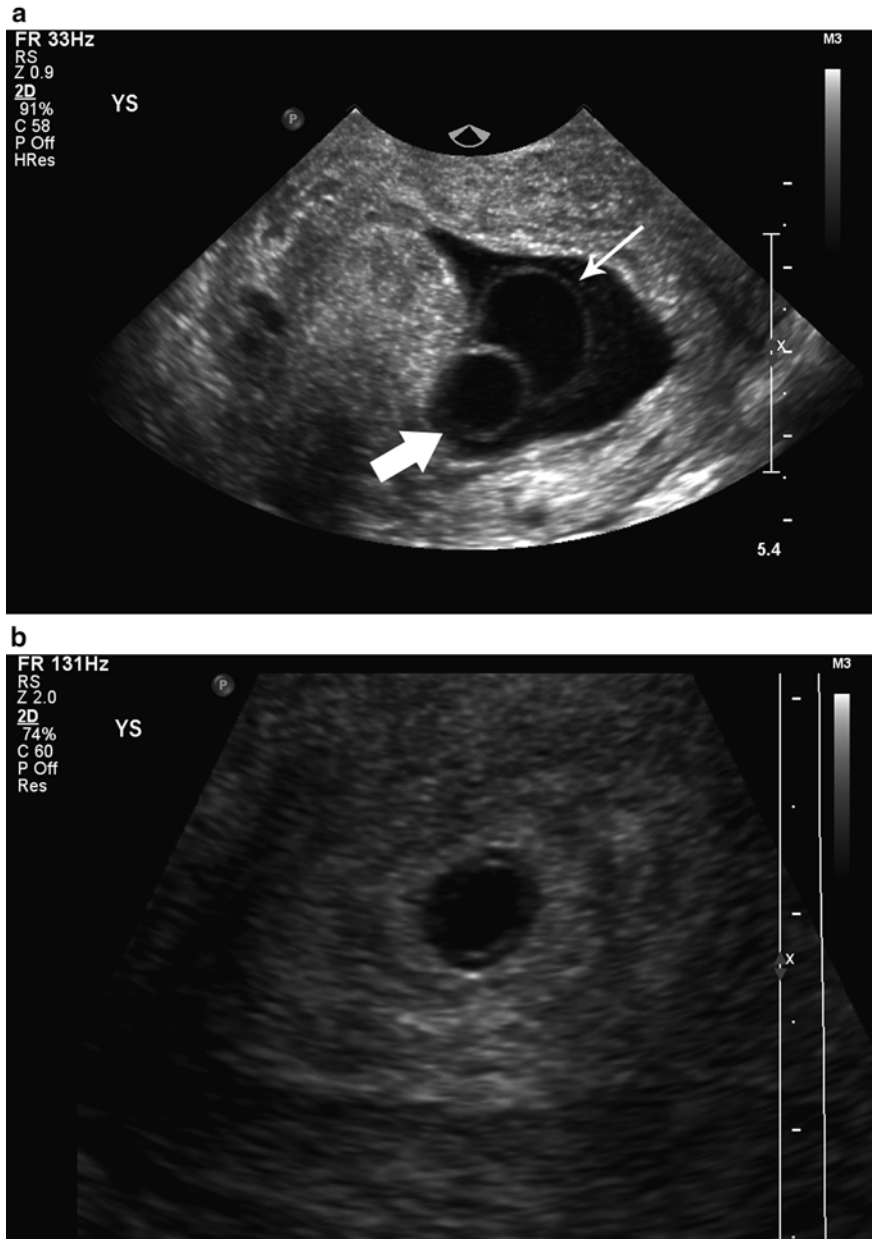

Fig. 15.17 (**a**) Large yolk sac. A large yolk sac (*thick arrow*) is seen compressing an empty amnion (*thin arrow*) at 6 weeks 1 day gestation in this transvaginal, midsagittal image. (**b**) Large yolk sac. A large yolk sac is visualized, filling the chorionic cavity in this axial, transvaginal image of a 4 week 1 day gestation

recently, Tan and colleagues followed 31 women with abnormal-appearing YSs and found no statistical association with pregnancy failure [44]. In many studies that identified abnormal-appearing YS, an embryo with cardiac activity continued normally to term. This raises concern that an abnormal YS is not consistently associated with pregnancy failure [44, 46, 49]. Therefore, an abnormal YS is, at best, a weak predictor of pregnancy failure.

An absent YS in the presence of an embryo has been associated with pregnancy loss in multiple

studies [46, 47]. An increased risk of pregnancy loss has also been reported in pregnancies with an enlarged yolk sac, but in many of these studies, normal pregnancies resulted despite an enlarged YS (Fig. 15.17a, b). Berdahl et al. followed 80 women with a YS diameter ≥5 mm and found a threefold increased risk of pregnancy loss compared to those with normal-sized yolk sacs [50]. Lindsay et al. found that an enlarged YS (greater than 2 standard deviations based on the gestational sac size) has a sensitivity and PPV for pregnancy loss of 15.6 % and 60.0 %, respectively [46]. Chama and coworkers found that a YS diameter more or less than 2 standard deviations from the mean, predicted pregnancy failure with a sensitivity, specificity, and PPV of 91.4 %, 66.0 %, and 88.8 %, respectively [51]. Lindsay et al. identified an association of a small YS (less than 2 standard deviations based on the gestational sac size) with pregnancy loss, giving a sensitivity and PPV of 15.6 % and 44.4 %, respectively [46]. However, a large yolk sac when identified with a viable embryo can exist in a normal pregnancy [47]. Based on these studies, a YS diameter greater than 2 standard deviations from the mean, in the absence of an embryo, would suggest pregnancy failure.

The presence of a YS within a gestational sac is reassuring; however, in the absence of an embryo, future viability is uncertain. Abdallah and associates followed 1060 pregnancies prospectively for viability. In the subgroup of pregnancies with a YS but without an embryo, the false-positive rate (FPR) to diagnose pregnancy failure was 2.6 % at a gestational sac diameter of 16 mm and 0.4 % at a cutoff of 20 mm, with no false positives when the gestational sac was ≥21 mm. Given the interobserver error, a cutoff of ≥25 mm was recommended to diagnose pregnancy failure when a YS is seen without an embryo [18].

Embryo

Observation of the location, appearance and activity of the embryo can provide clues to inevitable pregnancy failure. Abnormalities of embryonic size and growth have been closely linked with pregnancy failure.

Embryonic Motion

Embryonic motion can be visualized early in gestation by TVS and tends to be rapid jerking motions due to immaturity of the embryonic nervous system [24]. Goldstein et al. reported identification of embryonic body movements starting at 8 weeks gestation, with a sensitivity and PPV of 100 and 94.3 % [24].

Location

The embryo is first identified sonographically as a thickening along the YS. As the embryo grows, it assumes a C-shape and it begins to distance itself from the yolk sac, usually at around 55 days of gestation. The yolk sac maintains a thin connection to the embryo through the yolk stalk which can occasionally be visualized on TVS. The yolk stalk detaches from the midgut loop at the end of the sixth week of gestation (CRL of 8 mm) allowing the yolk sac to separate from the embryo. This separation continues until approximately the 10th–12th week of gestation when the YS begins to solidify and assumes a position between the amnion and chorion [52]. A loss of these anatomic relationships raises concern for potential pregnancy failure.

Filly and associates, in a retrospective review of the yolk stalk in embryos of 5 mm or less without cardiac activity, reported that premature separation of the embryo from the YS (evidence that the yolk stalk had developed—the "yolk stalk sign") was suggestive of an embryonic demise with a PPV of 100 % [53]. They theorized that visualization of the yolk stalk is not expected until a CRL of 8 mm when cardiac activity is expected. Hence, the lack of cardiac activity is further evidence of embryonic demise.

Appearance

The embryo has a classic appearance as it grows from a thickening along the YS into a fetus with recognizable head and limbs. Initial visualization of the embryo on TVS occurs when it reaches 2–3 mm in size and has the appearance of a straight echogenicity along the

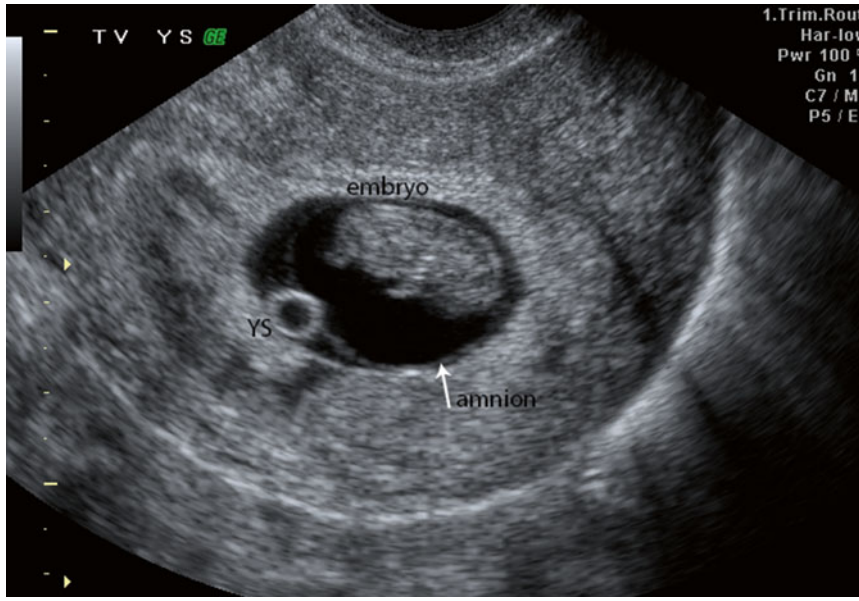

Fig. 15.18 Normal orientation of yolk sac, embryo and amnion. This transvaginal, axial image of the normal orientation of the yolk sac (YS), embryonic pole (CRL) and amnion are depicted

YS wall. At about day 21, the embryo develops a C-shape as the caudal neuropore elongates. At 24 days, a heart bulge can be seen, and by day 28, the embryo is 4 mm in length and limb buds appear. Distinct limbs may be visualized at about day 35 when the embryo measures 8 mm. A visible crown-rump length is not identified until about 49 days with the embryo measuring 18 mm (Fig. 15.18) [52].

There is no rigorous research assessing pregnancy outcomes in the absence of the above landmarks, but they may provide guidance clinically. A straight-appearing 4-mm embryo should raise concern for possible pregnancy failure, especially in the absence of cardiac activity prompting a follow-up exam. TVS has the potential to image the shape of the embryo, and this information can be used with other findings. Further study is ongoing, especially in the use of three-dimensional imaging, to evaluate the embryonic appearance and assess risk for pregnancy failure.

Size/Growth Rate

Multiple investigators have assessed embryo size compared to menstrual age in normal pregnancies and from this developed nomograms and regression formulas for embryonic growth. On average, these studies have supported a normal embryo growth rate of approximately 1 mm/day [54] (Fig. 15.19). A study by Bottomly et al. assessed embryonic growth and concluded that embryo growth is not linear, and their study questioned the reliability of an absolute growth rate for determining fetal viability [55]. Reljic found that when the CRL was greater than 2 standard deviations below the mean for expected gestational age, and ≤18 mm, there was a 6.5-fold increased risk of pregnancy failure compared to those at or above the mean. The risk of pregnancy failure increased as the discrepancy increased [56]. Reljic did not find a similar association when the CRL was >18 mm. A study by Stern and associates evaluating pregnancy failure after documentation of an embryonic heart rate (EHR) found that sonographic gestational age by CRL lagged by more than 0.6 weeks behind menstrual dates in 86 % of women studied [5]. Mukri et al. prospectively monitored the embryo/fetal growth in 292 pregnant women and found that there was a statistically significant difference between the

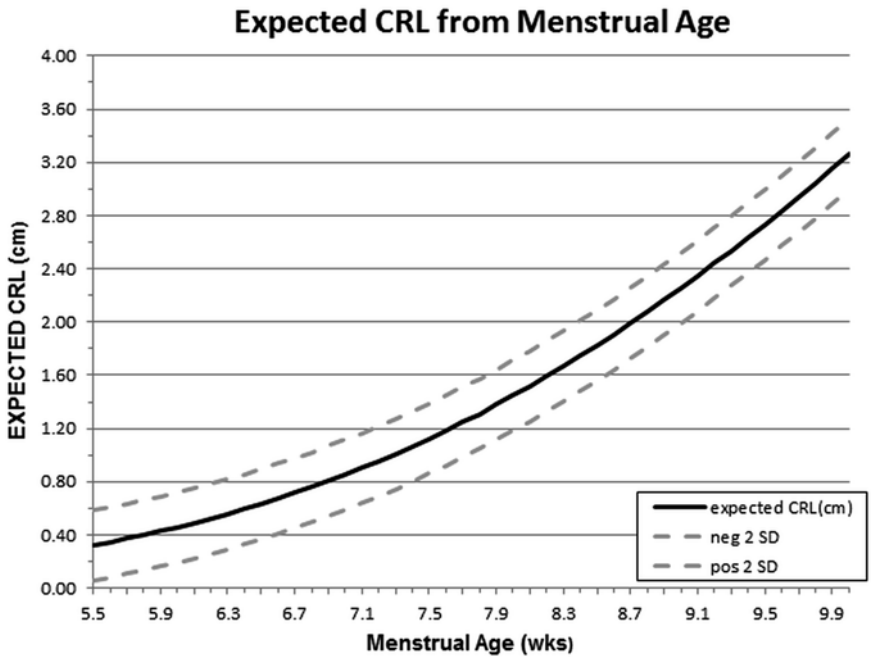

Fig. 15.19 The expected crown-rump length (CRL) in cm ± 2 standard deviation is compared to the menstrual age in weeks in this graph created with data from ref. [54]

gestational age by CRL compared to expected gestational age by LMP in pregnancies that ended in a demise by 11–14 weeks [57]. Sixty-one percent of the pregnancies that failed had CRLs that were more than 2 standard deviations below the mean; there was a direct relationship between an increasing discrepancy and the risk of pregnancy failure. At a threshold of 2 standard deviations below the mean, the sensitivity and PPV for pregnancy loss were 61 % and 31 %.

Numerous investigators have extensively evaluated a threshold CRL to definitively confirm an embryonic demise in the absence of cardiac activity. It is critically important to apply a threshold that provides accuracy and reliable reassurance to patients and takes into account interobserver error. Abdullah and associates in a prospective study evaluating CRL measurements in the absence of cardiac activity, determined false-positive rates in diagnosing pregnancy failure as 8.3 % using a CRL of 4.0 or 5.0 mm with no false positives found when using a CRL of ≥5.3 mm [22]. Accounting for inter- and intraobserver variation, a threshold CRL of ≥7 mm is recommended to diagnose pregnancy failure, when cardiac activity is not visualized.

Anatomy

Anatomic structural anomalies are now detected in the first trimester with increasing frequency (also see Chap. 19). An anomaly does not necessary predicate a pregnancy failure, but certain anatomic abnormalities may be associated with aneuploidy, which increases the risk of pregnancy failure. The sonologist should exercise caution, as there are developmental changes in the embryonic and early fetal periods that can be misinterpreted as anomalies (Figs. 15.20, 15.21, and 15.22). Table 15.2 lists some of the common first-trimester ultrasound pitfalls. Anomalies visualized in the first trimester are listed in Table 15.3 (Figs. 15.23, 15.24, 15.25, 15.26, and 15.27).

Embryonic Heart Rate

The EHR increases with gestational age, ranging from 90 to 113 bpm at 6 weeks gestation to a plateau of 140–170 bpm at about 9 weeks gestation [58]. Figure 15.28 depicts the mean EHR with +/−2

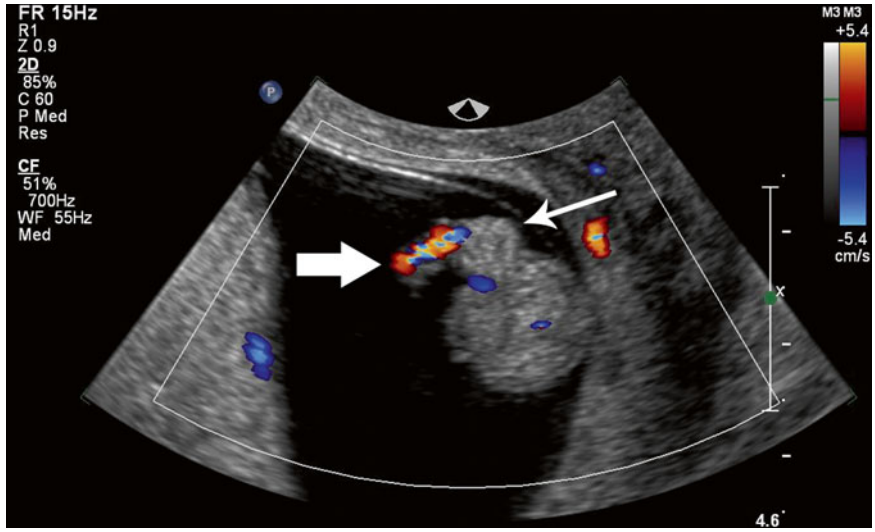

Fig. 15.20 Physiologic gut herniation. A physiologic herniation of fetal bowel (*thin arrow*) into the umbilical cord (*thick arrow*) is visualized in this transvaginal, midsagittal image of a 10 week 0 day fetus. This herniation was not seen at a 14 week follow-up exam

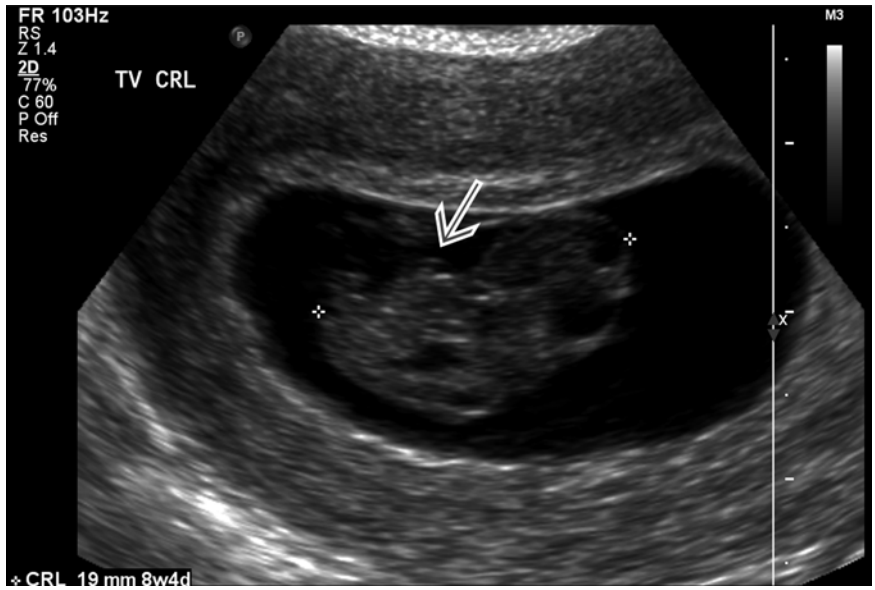

Fig. 15.21 Embryonic heart bump. The embryonic heart is noted as a "bump" (see *arrow*) in the mid torso of this normal 8 week 5 day embryo as seen in this transvaginal, axial image

standard deviations plotted against the crown-rump length for normal pregnancies [59, 60].

Multiple studies have determined that a low EHR, less than 85–100 bpm at a gestational age below 8 weeks gestation, is associated with pregnancy loss [58, 61–63]. The largest prospective study by Stefos and associates evaluated 2164 women and identified a threshold EHR of 85 bpm for predicting pregnancy loss at less than 6 weeks 3 days gestation. The threshold increased to 125 bpm between 7 weeks 4 days and 8 weeks 0 days [61]. With increasing gestational age, studies report an increase in the threshold EHR. Of note, the risk for pregnancy loss

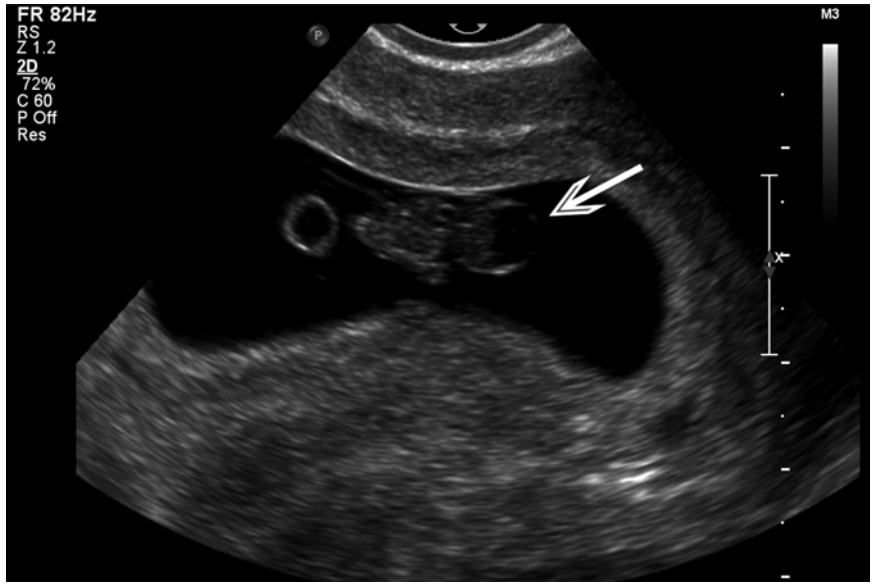

Fig. 15.22 Prominent rhombencephalon. Transvaginal, axial image of a normal 9 week 3 day fetus showing a prominent rhombencephalon mistaken for possible hydrocephalus. An 18-week fetal anatomy survey revealed normal intracranial anatomy

Table 15.2 Developmental pitfalls on first-trimester ultrasound

Ultrasound finding	Suspected anomaly	Normal embryonic development
Cystic space in the posterior cranium	Dandy walker malformation, hydrocephalus	Normal rhombencephalon
Mass at the fetal umbilical cord insertion	Omphalocele	Physiologic herniation of the fetal bowel
Embryonic heart seen as a mass on the chest	Ectopic cordis	In the early embryo the heart is normally an anterior chest bump

Table 15.3 Anomalies identified on first-trimester ultrasound

Anencephaly
Bladder outlet obstruction
Conjoined twins
Cystic hygroma
Encephalocele
Gastroschisis
Holoprosencephaly
Limb-body wall defect
Omphalocele/abdominal wall defect

increases as the EHR decreases, especially between 6 and 9 weeks gestation [61, 64, 65]. A slow EHR (<90 bpm) when observed at 6–7 weeks gestation, carries a risk of first-trimester pregnancy loss of about 25 % in several studies even in cases where the EHR is in the normal range at an 8-week follow-up exam [64, 65]. An increased EHR (greater than 2 standard deviations above the mean) has not been associated with pregnancy loss [64].

Aneuploidy has been linked to abnormal fetal heart rates (FHR) [66–68]. Liao and associates retrospectively evaluated 25,000 women who underwent first-trimester screening and found that fetuses with trisomy 21, trisomy 13 and Turner syndrome had an increased probability of a FHR greater than 2 standard deviations above the mean (9.7 %, 67.4 % and 52.2 %, respectively), while fetuses with trisomy 18 and triploidy had an increased probability of a decreased FHR more than 2 standard deviations below the mean (18.7 % and 30.0 %, respectively) [68].

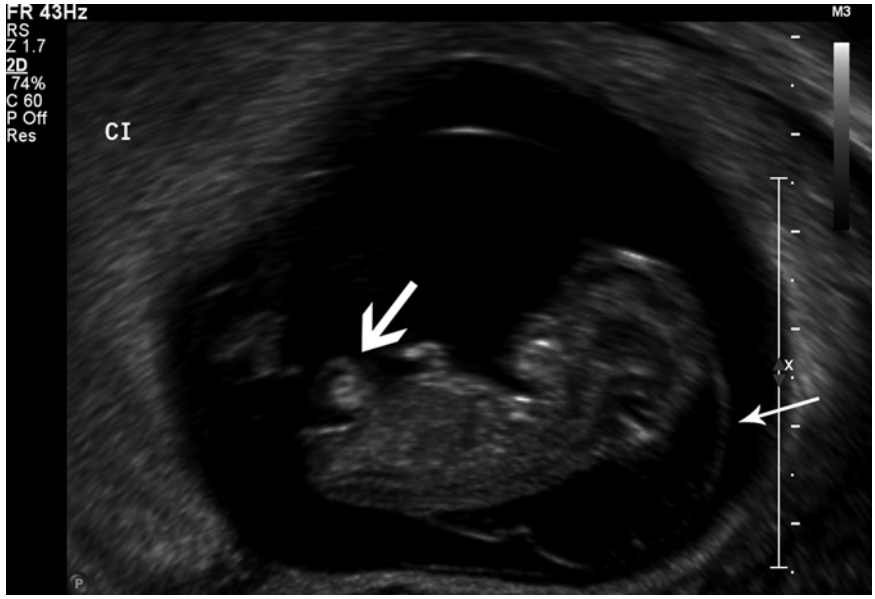

Fig. 15.23 Omphalocele. An omphalocele (*thick arrow*) is noted with a thickened nuchal translucency (*thin arrow*) in this transvaginal, axial image of an 11 week 4 day fetus

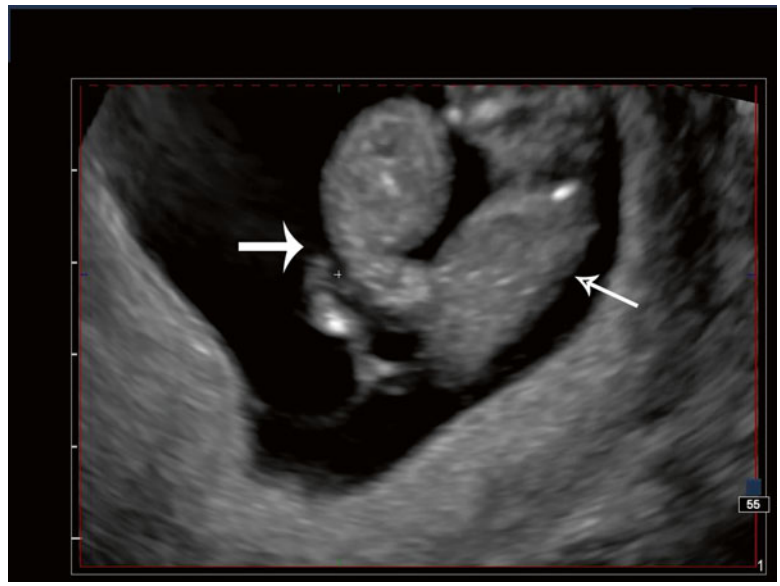

Fig. 15.24 Conjoined twins. The *thin arrow* depicts Fetus A and the *thick arrow* Fetus B in this transvaginal, midsagittal image of omphalopagus conjoined twins at 11 weeks 0 days gestation

Retained Products of Conception

Retained products of conception (RPOC) are the persistence of placental and/or fetal tissue in the uterus, following a miscarriage, termination of pregnancy or delivery. It complicates 1 % of pregnancies and is most common after medical termination of pregnancy and second trimester miscarriage. The most common patient complaints associated with RPOC are vaginal bleeding, pelvic pain, and/or fever. Abbasi and colleagues found that vaginal bleeding had the highest

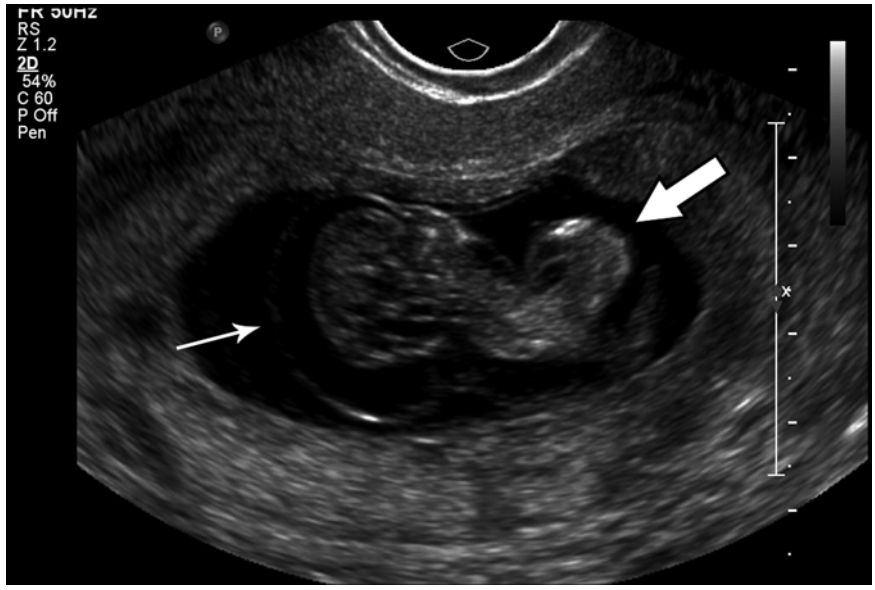

Fig. 15.25 Thoracoabdominal wall defect. Transvaginal, axial image of an 11 week fetus showing a defect in the thoracoabdominal wall (*thick arrow*) with the heart and bowel contents herniating from the fetus. A thickened nuchal translucency (*thin arrow*) is also noted

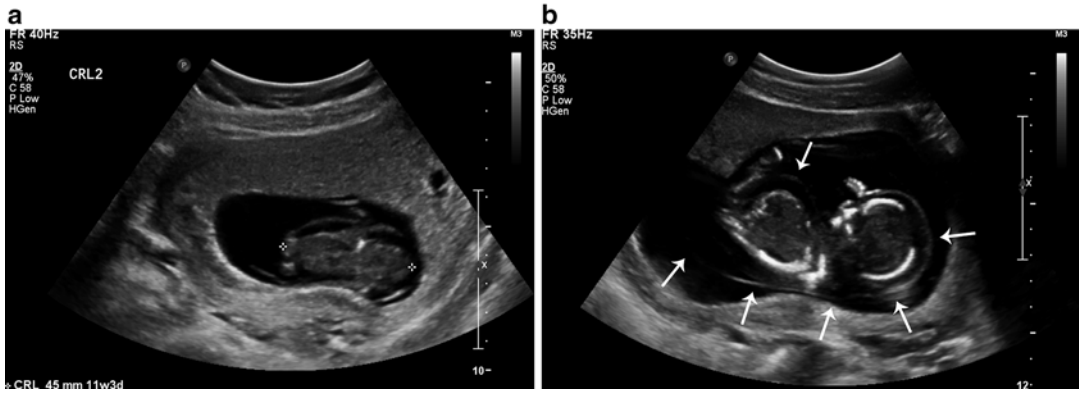

Fig. 15.26 (**a**) Fetal anasarca. This transvaginal, axial image shows an 11 week 6 day fetal demise (calipers) with anasarca found to be triploidy by karyotype. (**b**) Fetal anasarca. A 13 week 6 day fetal demise with anasarca (*arrows*) is visualized in this transvaginal, longitudinal image also showing a thickened nuchal translucency. A karyotype of the products of conception revealed trisomy 13

sensitivity and specificity for RPOC of 93 % and 50 %, respectively [69].

Ultrasound Evaluation

Clinical evaluation for RPOC is inaccurate, therefore, TVUS is frequently chosen for definitive evaluation. Sadan et al. reported that the presence of hyperechoic or hypoechoic material within the uterine cavity or an endometrial lining thicker than 8 mm had a PPV of 71 % for histologically confirmed RPOC [70]. Durfee and associates found that an endometrial mass was the most sensitive and specific sonographic feature of RPOC (79 % and 89 %, respectively), with a PPV of

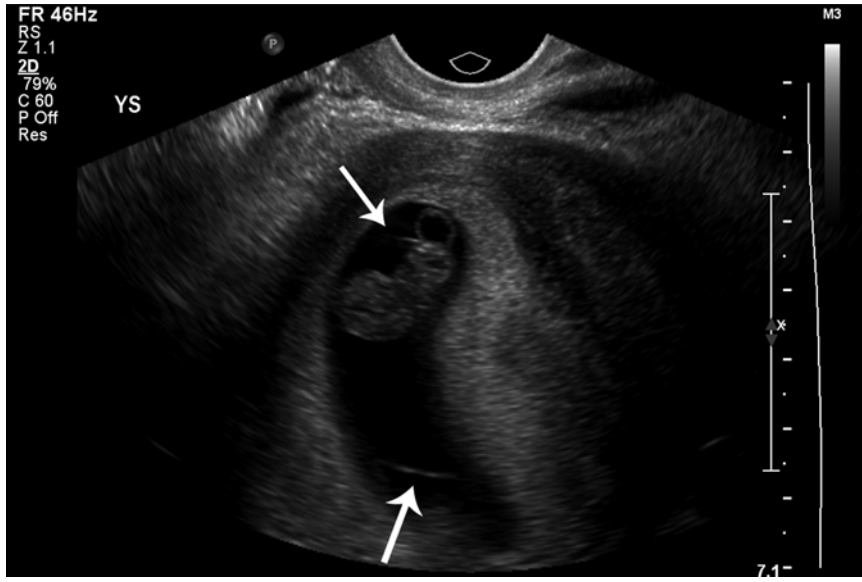

Fig. 15.27 Large amnion with abnormal-appearing fetus. A 9 week 4 day abnormal-appearing fetus with an enlarged amnion (*arrows*) is visualized by transvaginal imaging in the axial plane. Cardiac activity is not visualized when cardiac activity was previously demonstrated. The fetal karyotype was 45X

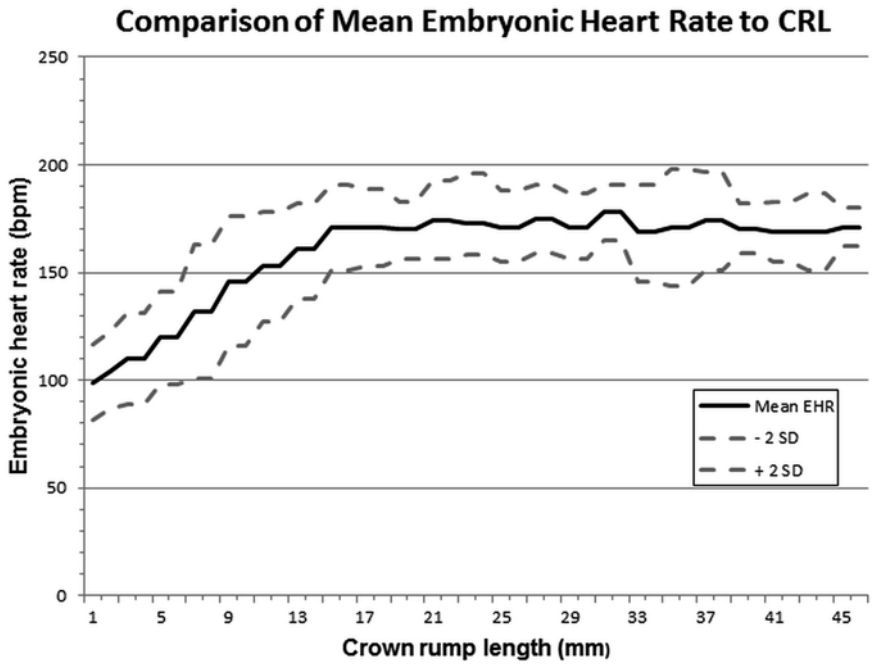

Fig. 15.28 The graph shows the comparison of the embryonic heart rate in bpm ± 2 standard deviations to the crown-rump length in mm created with data from refs. [59] and [60]

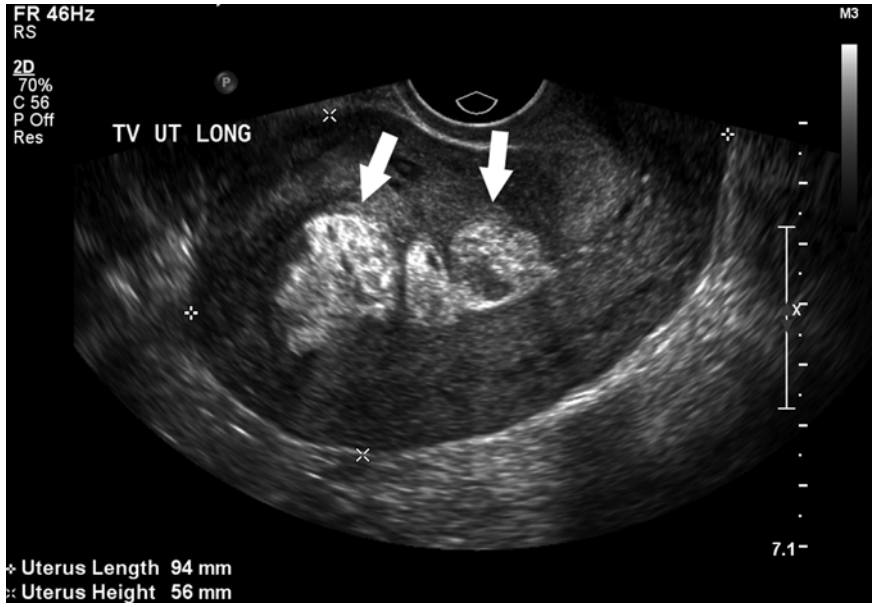

Fig. 15.29 This is a longitudinal transvaginal image of a 39-year-old woman who presented to the emergency room complaining of vaginal bleeding and pelvic pain at 10 weeks 5 days pregnant. A previously identified gestational sac and fetus are not seen. The *arrows* identify echogenic masses within the uterine cavity

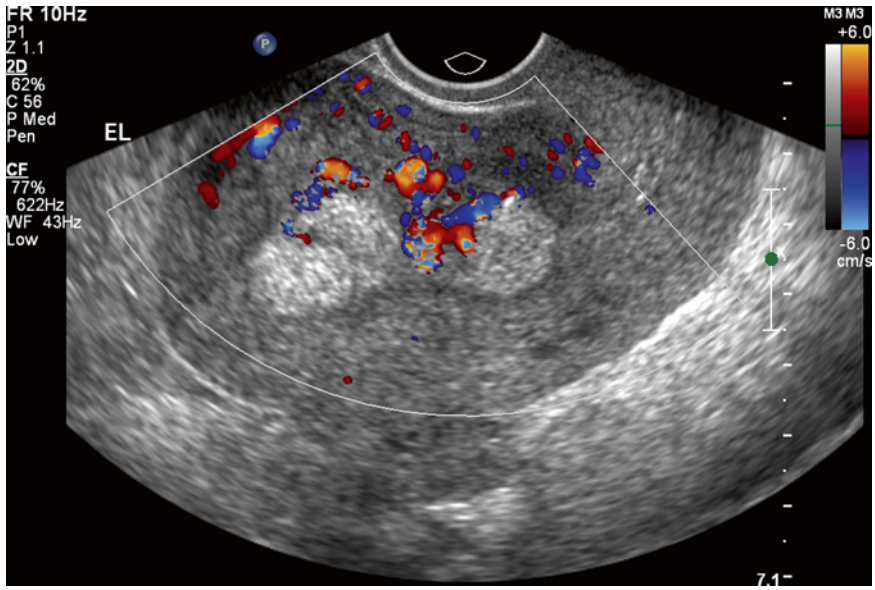

Fig. 15.30 A longitudinal, transvaginal, color Doppler image is depicted of the same patient described in Fig. 15.29. Vascular flow is demonstrated within the echogenic masses. The pathology from a dilatation and curettage revealed retained products of conception

59 % [71] (Fig. 15.29). An endometrium lining greater than 10 mm, as an isolated finding, had low sensitivity and specificity and was detected more frequently in patients without RPOC. Durfee et al. also found that complex fluid alone, identified within the uterine cavity, was a poor predictor of RPOC, and the absence of sonographic findings had a NPV for RPOC of 100 % [71].

Color Doppler Imaging

Color Doppler mapping of the uterine cavity is advocated to further evaluate the uterine cavity for RPOC (Fig. 15.30). Durfee and associates found that blood flow in the endometrium had a PPV of 75 % for the presence of RPOC, but a NPV of 46 %. They concluded that color Doppler imaging was not helpful for predicting RPOC [71]. Kamaya et al. graded the endometrial vascularity, in women referred for suspected RPOC, by color Doppler imaging. The endometrium was graded from type 0, no detectable vascularity, to type 3, marked vascularity [72]. They found that detectable vascularity of any type (1–3) had a high likelihood of RPOC, with a PPV of 96 %. All women with types 2 and 3 vascularity were found to have RPOC, while type 0 vascularity did not exclude RPOC. These findings suggest that color Doppler mapping of the uterine cavity can improve the sensitivity and PPV for predicting RPOC.

Recurrent Pregnancy Loss

Recurrent pregnancy loss (RPL) is most commonly defined as two or more failed pregnancies, which have been documented by ultrasound or histopathological examination [73]. It occurs in less than 5 % of women, with 1 % having three or more pregnancy losses. There are multiple suspected etiologies, with cytogenetic (2–5 %), antiphospholipid syndrome (8–42 %) and anatomic anomalies (1.8–37.6 %) comprising the majority of causes. Congenital uterine anomalies are present in 12.6 % of women with RPL and can be characterized by 3-D ultrasound imaging. The highest rates of RPL are present in women with congenital uterine anomalies: septate (44 %), bicornuate (36 %), and arcuate (26 %) uteri [73]. Despite these findings, a definitive diagnosis for RPL is determined in only 50 % of women. The mechanisms of RPL are not completely understood and research is ongoing.

In the absence of a definitive etiology, treatment is very limited. However, Brigham and associates reported that despite three consecutive miscarriages, 70 % of women with idiopathic RPL conceived and 55 % went on to have fetal survival beyond 24 weeks gestation [74]. No statistical difference in outcome between women with two and those with three previous losses was found. In addition, 78 % of miscarriages in women with recurrent losses were identified between 6 and 8 weeks gestation, and in 89 %, cardiac activity was never visualized [74]. Cardiac activity at 8 weeks was associated with a 98 % chance of successful pregnancy that increased to 99.4 % when cardiac activity was demonstrated at 10 weeks gestation.

Summary

Ultrasound assessment of the first-trimester pregnancy has dramatically improved the diagnostic capabilities of clinicians over the past four decades. Once a hidden, mysterious part of pregnancy, the first trimester is now open to investigation and examination. Imaging the stages of embryonic and fetal development provide the clinician with valuable information which can be used to screen for aneuploidy, evaluate for anomalies and identify markers of fetal viability. The best predictors of pregnancy failure are the absence of an embryo once the mean gestational sac size reaches 25 mm and the absence of cardiac activity once the embryo is ≥7 mm. These thresholds are justifiably conservative but allow us to reassure our patients with confidence of the sonographic diagnosis of pregnancy failure.

Teaching Points

- The β-hCG discriminatory level to visibly confirm an intrauterine pregnancy by transvaginal ultrasound is 4000 mIU/mL.
- An empty gestational sac with a mean sac diameter of ≥25 mm is considered anembryonic.
- An embryo without cardiac activity at a crown-rump length of ≥7 mm is considered an embryonic demise.
- A fetal heart rate <90 bpm at >6 weeks gestation is concerning for impending pregnancy failure.

- A gestational sac or embryo that does not grow 1 mm/day over 7–10 days is concerning for pregnancy failure.
- Absence of a viable embryo ≥2 weeks after identification of a gestational sac without a yolk sac is anembryonic.
- Absence of a viable embryo ≥11 days after identification of a gestational sac with a yolk sac is anembryonic.
- 60 % of spontaneous abortions at <12 weeks gestation are due to chromosomal abnormalities.
- The diagnosis of retained products of conception can be suspected when hyperechoic or hypoechoic material is visualized within the uterine cavity or the endometrial lining is thicker than 8–10 mm, although the positive predictive value is less than optimal. Color Doppler may be helpful in these situations.
- A definitive etiology for recurrent pregnancy loss is determined in only 50 % of women and, in the absence of a conclusive diagnosis, treatment is very limited

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Ectopic Pregnancy: Pregnancy of Unknown Location (PUL)

16

Linda Do and James M. Shwayder

Introduction

Ectopic pregnancy (EP) represents 1–2 % of pregnancies [1]. They have a risk of rupture, hemorrhage, and tubal damage, which can lead to decreased future fertility and even death. The most common presenting symptoms suggesting an EP are abdominal pain or vaginal bleeding. Advances in ultrasound technology allow the detection of ectopic pregnancies in their earliest state, allowing treatment alternatives, e.g., medical therapy or surgical treatment, and reduced morbidity and mortality. However, immediate diagnosis is not always accomplished. Thus, a systematic approach to patients with a possible EP is required to avoid interruption or mistreatment of an intrauterine pregnancy (IUP), timely diagnosis of an EP, and appropriate management with pregnancy failure. This chapter reviews such an approach emphasizing the value of various diagnostic tests.

Pregnancy of Unknown Location

Pregnancy of unknown location (PUL) describes a situation in patients with a positive pregnancy test when transvaginal ultrasound (TVS) fails to identify a pregnancy's location, either intrauterine or extrauterine. In patients with a positive urinary pregnancy test, the location of a pregnancy is usually confirmed in more than 90 % of cases [2]. The remainder is categorized as a PUL [3]. In 2011, Barnhart et al. reviewed the consensus nomenclature associated with early pregnancy evaluation, categorizing such pregnancies into the following descriptive areas [4]:

- Definite ectopic pregnancy,
- Probable ectopic pregnancy,
- Pregnancy of unknown location,
- Probable intrauterine pregnancy, or
- Definite intrauterine pregnancy.

The earliest sign of pregnancy is the finding of a sac-like structure, regardless of location. The finding of such a structure in the uterus is considered a probable IUP. This same finding in the adnexa is consistent with a probable EP. The finding of a yolk sac within a gestational sac definitively diagnoses a pregnancy, regardless of location. The finding of a gestational sac with a yolk sac in the uterus is consistent with a definite IUP, while this same finding outside of the uterus definitely diagnoses an EP. A PUL exists when there are no signs of either an IUP or an EP, which represents ~10 % of cases [5]. Expectant management with TVS and hCG will lead to the diagnosis of a visualized IUP (34.3 %) or EP (8.7 %), with a resolved PUL in

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56.9 % of these patients [5]. Thus, patients who are clinically stable with a PUL should be managed expectantly [3]. A small number of patients will remain with a PUL, which can be treated medically, surgically, with a diagnostic dilatation and curettage, or observed for spontaneous resolution [4].

A consensus regarding follow-up surveillance of patients with a PUL has not been obtained. Individualized surveillance based on risk factors could lead to more accurate diagnosis and reduced cost. Barnhart et al. retrospectively assessed specific clinical factors to determine the frequency and immediacy of follow-up for patients with a PUL [6]. They created a scoring system to triage women into various risk groups. Those at age "extremes" were assigned increasing risk scores: age < 18 received a +1 and age > 38 assigned a +3. Prior EP increased a patients risk, with those having one prior EP assigned +2, whereas those with 2 or more prior EP were assigned +3. Patients with bleeding were assigned +4. Patients with a prior miscarriage or with a hCG > 2000 mIU/mL were assigned −1. A patient's risk for a nonviable gestation was stratified into low risk (−2 to −1), intermediate risk (0 to +4), and high risk (equal to or greater than +5) based on the total score. Based on their risk stratification, patients received surveillance as follows:

- low-acuity surveillance: "send home" with follow-up in 4–7 day
- standard surveillance; "monitor" with repeat hCG in 2 days, or
- high-acuity surveillance: "intervention" including uterine evacuation, laparoscopy, or surveillance in 24 h, depending on the patient's clinical status.

Overall, the proposed scoring system had a >90 % specificity. Thus, clinical signs and symptoms of a woman with PUL may help optimize surveillance plans.

Condous et al. developed a logistic regression model using serial hCG and progesterone levels, drawn 48 h apart, to predict the outcome of PULs. A hCG increase of >66 % was predictive of an IUP with a positive predictive value (PPV) of 96.5 %. A serum progesterone of <20 mmol/l predicted a failing PUL with a PPV of >95 %. In summary, the change in hCG outperformed serum progesterone change in predicting the location and outcome of a PUL.

One can postulate that combining the results of these two studies would improve our surveillance of patients with PUL. Specifically, individualized risk assessment, correlated with serial hCG levels, and complimented with ultrasound and, in select cases, serum progesterone will help determine the ultimate outcome of PULs.

Human Chorionic Gonadotropin (hCG) Dynamics

Human chorionic gonadotropin (hCG) can be qualitatively assessed resulting in a positive or negative result. However, measuring the quantitative hCG level in the blood is quite useful if the initial pregnancy evaluation is inconclusive. One can follow serial hCG levels, using the rationale that abnormally rising levels are more consistent with either an EP or a failed IUP. Older studies determined that the 2-day rise of hCG in a normal pregnancy is at least 66 % [7]. A more recent 2004 study determined that the 2-day rise hCG (normal pregnancy) ranged between 1.53 and 3.28 times, with a median of 2.24 times [8]. The premise is that an ectopic pregnancy will have an inadequate rise in the hCG level over 2 days, as only 21 % of EPs will have a rise of 53 % or more [9]. An often overlooked finding of the earlier study was that 15 % of normal pregnancies also had abnormal hCG increases. Thus, abnormally rising hCG levels are not diagnostic of an ectopic pregnancy, only highly suggestive. Abnormal increases in hCG values should raise one's index of suspicion for an ectopic pregnancy or an abnormal intrauterine pregnancy. TVS is valuable, regardless of hCG increase, to determine the location and status of the pregnancy.

Threshold and Discriminatory Levels of hCG

Threshold Level

The threshold level is the lowest level of hCG at which a normal intrauterine pregnancy can be detected, typically visualizing an early gestational sac. Older studies proposed a threshold value of 1000 mIU/mL [10]. However, advances in ultrasound technology have improved our imaging capabilities. Thus, more recent studies indicate the threshold level may be as low as 390 mIU/mL [11].

Discriminatory Level

The discriminatory level is that level of hCG above which all normal (singleton) intrauterine pregnancies should be seen. This level typically ranged between 1000 and 1500 mIU/mL in most laboratories. The discriminatory level or value, however, has undergone revision, based on two key studies. Doubilet and Benson reviewed a decade of experience in patients with TVS and hCG done on the same day [12]. They identified those patients whose initial TVS did not visualize an intrauterine fluid collection, with embryonic or fetal cardiac activity found on subsequent ultrasound studies. They demonstrated that slightly more than 10 % of patients with an IUP ultimately diagnosed had an initial hCG ≥ 1500 mIU/mL (5.9 % with levels of 1500–1999 mIU/mL; 4.5 % > 2000 mIU/mL) (Table 16.1). Connolly et al. performed a similar study including patients who had a TVS and hCG within 6 h of each other. They tabulated the levels associated with 99 % of IUPs. In this study, the discriminatory level was 3510 mIU/mL (Table 16.2). The current recommendation with an inconclusive ultrasound, assuming the patient is hemodynamically stable, is to follow the patient until the hCG level is at least 3000–3500 mIU/mL before declaring that an IUP is not visualized. This would defer medical intervention, such as methotrexate, until the diagnosis is clarified. This recommendation will largely avoid the inadvertent treatment of an IUP with methotrexate, with resultant fetal anomalies or fetal loss [13]. These hCG levels and recommendations pertain only to singleton pregnancies. Multiple gestations often have much higher hCG levels before identifying the intrauterine gestations. Thus, caution is advised in patients who have undergone assisted reproduction.

Table 16.1 Evidence against the hCG discriminatory level [12]

hCG (mIU/mL)		
Third–Fourth international standard	# (202)	%
<1000	162	80.2
1000–1499	19	9.4
1500–1999	12	5.9
≥2000	9	4.5

Endometrial Findings in Ectopic Pregnancy

Endometrial Thickness

When a gestational sac or yolk sac are not visualized, endometrial thickness may be helpful in assessing the location of a pregnancy. Spandorfer and Barnhart reviewed the ultrasound measured endometrial thickness in patients with a hCG below the discriminatory level. In general, an IUP had a mean endometrial thickness that was greater than an EP or a spontaneous miscarriage (13.42 mm vs. 5.95 mm vs. 9.28 mm, respectively) [14]. In their study, an endometrial thickness ≤ 8 mm was associated with an abnormal pregnancy in 97 % of cases. Thus, when evaluating early pregnancy, a thicker endometrium may be more commonly associated with an IUP, while a thinner endometrium is more common with an EP (Figs. 16.1 and 16.2).

Table 16.2 Reevaluation of the threshold and discriminatory levels [11]

hCG (mIU/mL)	Gestational Sac	Yolk Sac	Embryo
Threshold level	390	1094	1394
Discriminatory level	3510	17,716	47,685

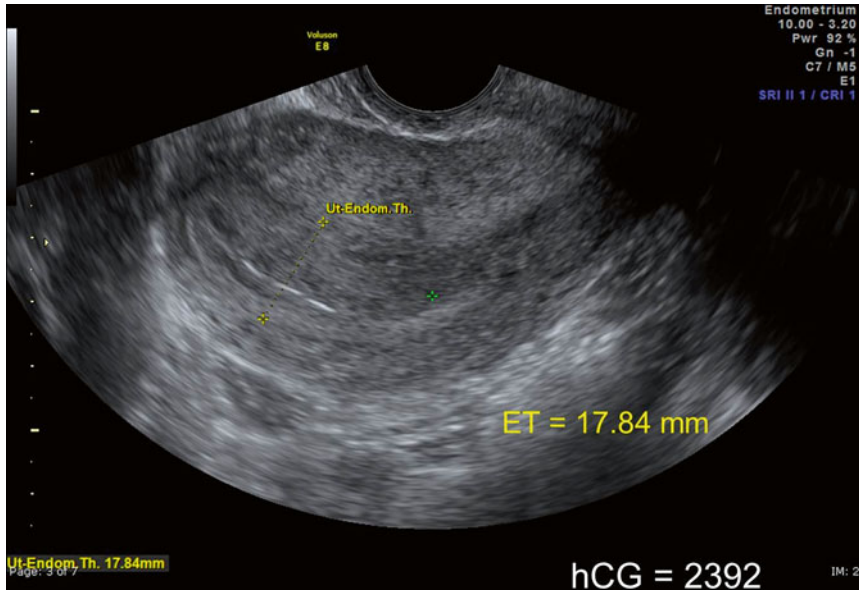

Fig. 16.1 Thicker endometrium (17.84 mm) in an early intrauterine pregnancy

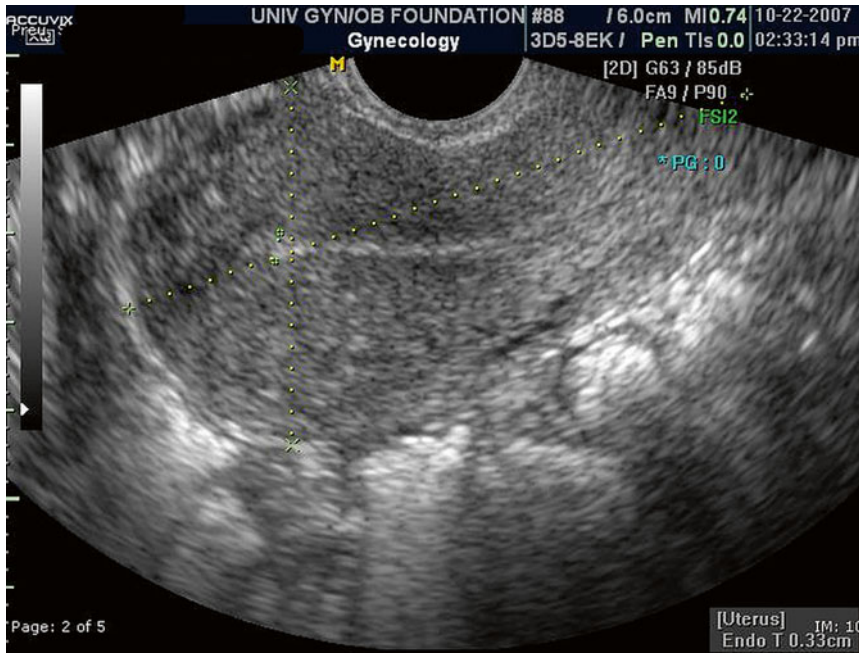

Fig. 16.2 Thin endometrium (3.3 mm) associated with an ectopic pregnancy

Intrauterine Fluid

The characteristics and shape of the intrauterine fluid in early pregnancy helps determine a pregnancy's location. Benson et al. determined that no intrauterine fluid was present in 83.4 % of patients with an EP (191 of 229) [15]. Furthermore, 86.8 % of those patients with an EP and intrauterine fluid (33 of 38), also had an adnexal mass. In most of these patients (31 of 38, or 81.6 %), the fluid that was present tended to follow the contour of the endometrial cavity (Fig. 16.3).

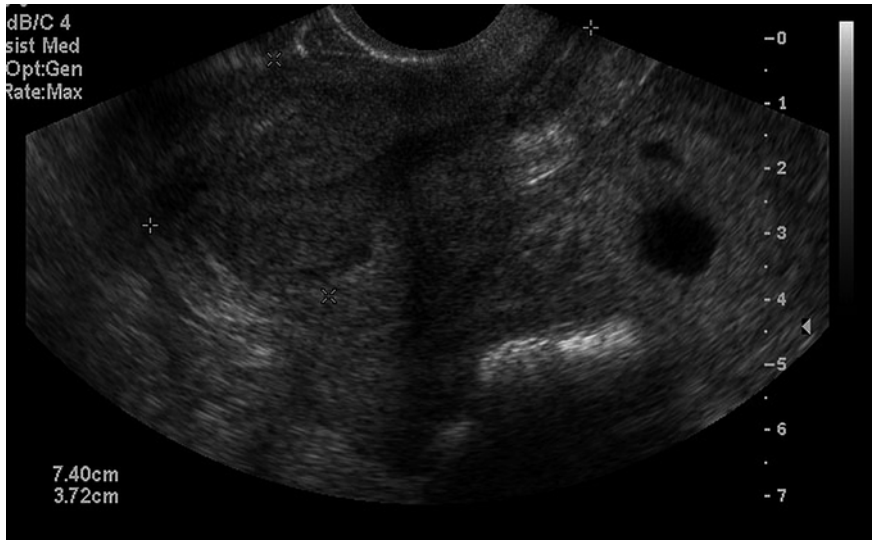

Fig. 16.3 Intrauterine fluid with low-level echoes following the endometrial contour in patient with an ectopic pregnancy

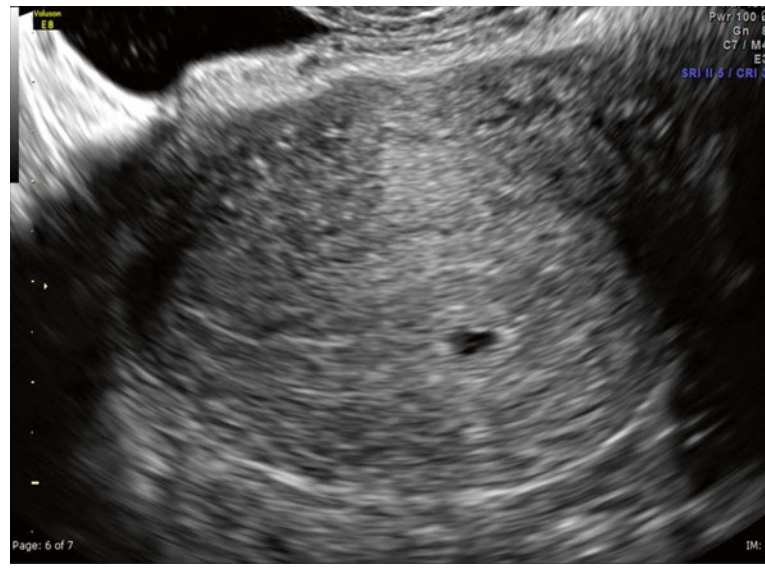

Fig. 16.4 Gestational sac located in the posterior endometrium in an early intrauterine pregnancy

A smaller number (7 of 38, or 18.4 %) had a smooth walled cyst-like structure within the uterus. Such a cystic fluid collection can mimic an IUP. The differentiation is that the gestational sac of an IUP burrows into the decidua and is located slightly eccentrically (Fig. 16.4). One of the most important findings of this study was that a smooth-walled anechoic intrauterine cystic structure with no identified adnexal mass is associated with an IUP in 99.8 % of patients (Fig. 16.5).

Adnexal Findings in Ectopic Pregnancy

In 1994, Brown and Doubilet reviewed ten studies with over 2000 patients with suspected EP to determine the adnexal findings associated with an ectopic pregnancy [16]. All ectopic pregnancies were surgically confirmed. They determined the following four categories of adnexal findings associated with ectopic pregnancies:

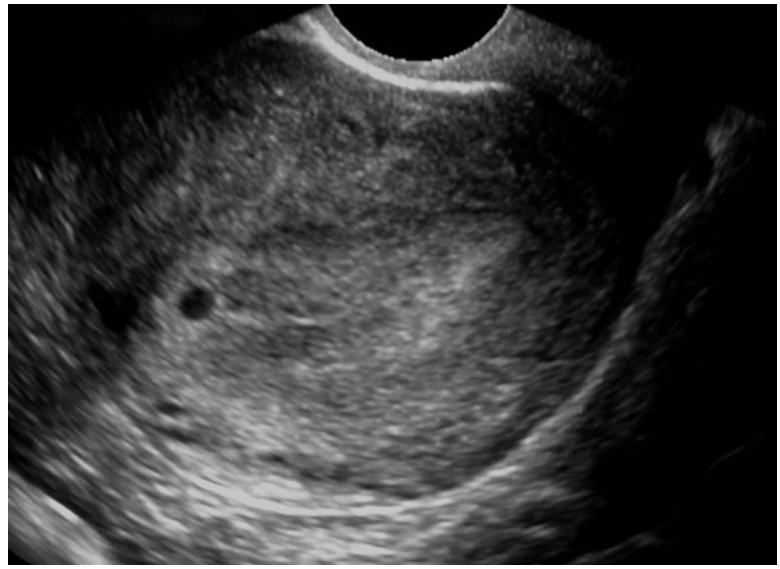

Fig. 16.5 Smooth-walled anechoic sac in a patient with an early IUP

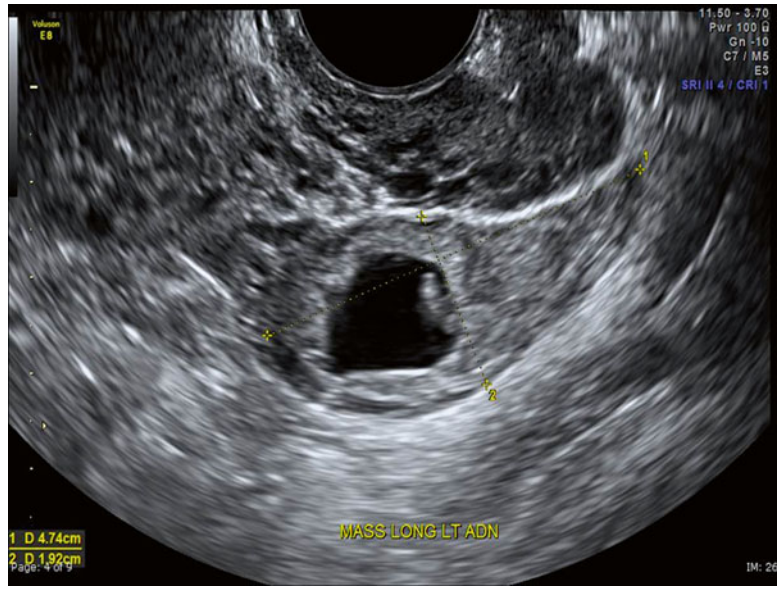

Fig. 16.6 Adnexal embryo with FHR = 172 which is diagnostic of an ectopic pregnancy

1. An adnexal embryo with a heartbeat (Fig. 16.6);
2. An adnexal mass with a yolk sac and no embryonic cardiac activity (Fig. 16.7);
3. An adnexal mass with a central anechoic area with a hyperechoic ring ("tubal ring" or the "bagel sign") (Fig. 16.8); and
4. Any adnexal mass, other than a simple cyst or an intraovarian lesion (Fig. 16.9).

The first two findings are diagnostic of an EP. The tubal ring is associated with an ectopic pregnancy in 95 % of cases. Any complex or solid adnexal mass that is not intraovarian is associated with an ectopic pregnancy in 92 % of cases (Table 16.3). Such adnexal findings are present in almost 95 % of EP with each finding being visualized in 7.4 %, 8.3 %, 24.7 %, and 54.1 % (respectively) of EP [17].

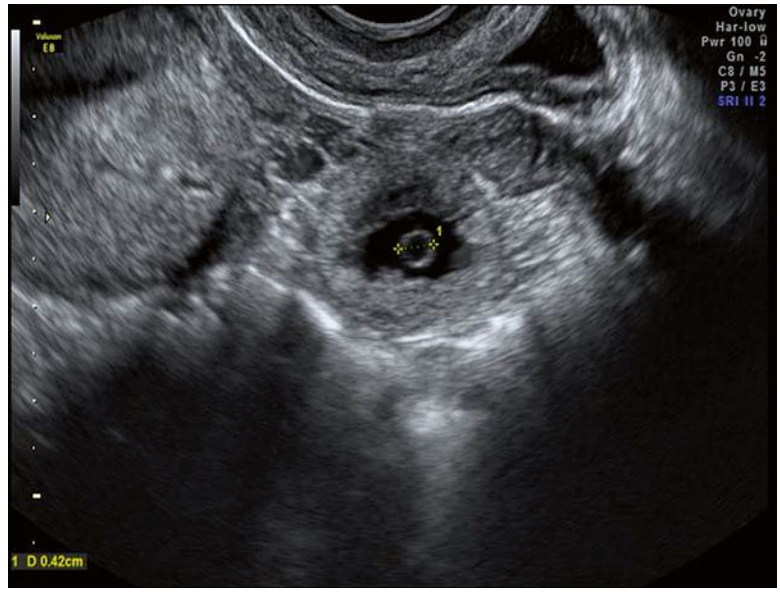

Fig. 16.7 Adnexal mass with a yolk sac which is diagnostic of an ectopic pregnancy

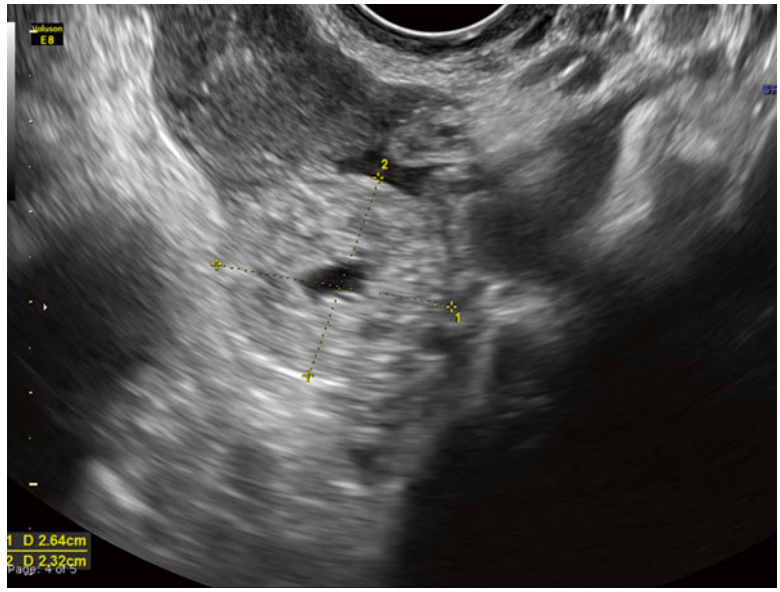

Fig. 16.8 "Tubal ring," or so-called "bagel sign" in an ectopic pregnancy

Work-Up for Ectopic Pregnancy

This chapter reviews the hCG and ultrasound findings in ectopic pregnancy. The order in which one performs various tests, including serum progesterone, in patients with suspected EP was evaluated by Garcia and Barnhart in a 2001 paper [18]. The order of these tests included the following:

- Ultrasound followed by quantitative hCG if the ultrasound findings were inconclusive
- Quantitative hCG followed by ultrasound, when the hCG was >threshold value
- Progesterone followed by ultrasound and, if inconclusive, then quantitative hCG
- Progesterone followed by quantitative hCG and, when >threshold value, then ultrasound
- Ultrasound followed by repeat ultrasound
- Clinical examination only

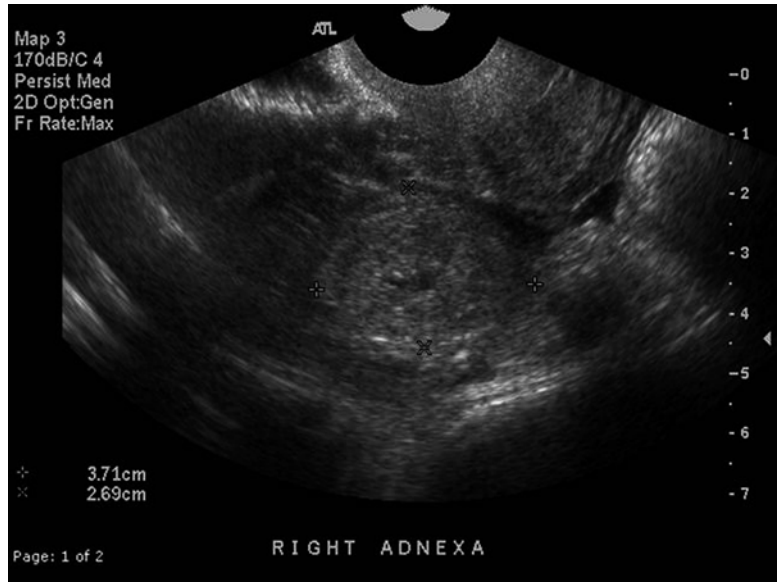

Fig. 16.9 Adnexal mass separate from the ovary in an ectopic pregnancy

Table 16.3 Adnexal criteria for ectopic pregnancy [16, 17]

Adnexal finding on TVS	Likelihood of ectopic (%) [16]	Frequency of findings [17]
Extrauterine embryo with cardiac activity	100	7.4
Adnexal mass with yolk sac without embryonic cardiac activity	100	8.3
Adnexal mass with central anechoic area and hyperechoic rim ("tubal ring")	95	24.7
Any complex or solid adnexal mass other than a simple cyst or intraovarian lesion	92	54.1

They applied these algorithms to a theoretical cohort of 10,000 patients determining the number of ultrasounds, blood draws, dilatation and curettages, and laparoscopies performed. They then predicted the costs of the various strategies, and their effectiveness in diagnosing Eps. (Table 16.4). Ultimately they recommended either of the first two strategies, as the progesterone methods missed more ectopic pregnancies, the ultrasound only strategy was too costly, and the clinical exam only method to ineffective. Of note, although serum progesterone may be helpful in predicting viability of a pregnancy [19], the Garcia study confirmed the findings of others that progesterone lacks adequate sensitivity in distinguishing ectopic and intrauterine pregnancies [20–22].

An Argument for Ultrasound First, Tubal Rupture Below the Threshold Level

The Connolly study previously discussed determined the threshold level of hCG should be lowered to 390 mIU/mL [11]. Prior to this study, many practitioners deferred ultrasound until the hCG level was $\geq$ 1000 mIU/mL. However, an early study by Saxon et al. demonstrated that 50 % of ruptured EPs had a hCG $\leq$ 999 mIU/mL [23]. This finding was confirmed by the 2014 report of Frates et al. also demonstrating that half of ruptured EPs had a hCG < 1000 mIU/mL. Thus, in patients with suspected EP, with bleeding, pain, and a positive qualitative pregnancy test, performing ultrasound first has value in identifying a definite IUP, EP, or a significant hemoperitoneum (Fig. 16.10). Not visualizing a significant hemoperitoneum allows a more conservative evaluation of such patients, while assuring patient safety.

Table 16.4 Six strategies for diagnosing ectopic pregnancy [18]

Strategy	Days to Dx	Blood draws/10,000	Total charge per patient	Missed EP per 10,000	Interrupted IUP per 10,000
Ultrasound → hCG	1.46	5227	$1958	[0]	70
hCG → Ultrasound	1.66	14,375	$1842	0	122
P → Ultrasound → hCG	1.25	12,108	$1692	24	25
P → hCG → Ultrasound	1.26	15,003	$1569	24	39
Ultrasound → Ultrasound	1.21	0	$2486	0	121
Clinical exam only	1.0	0	$0	940	0

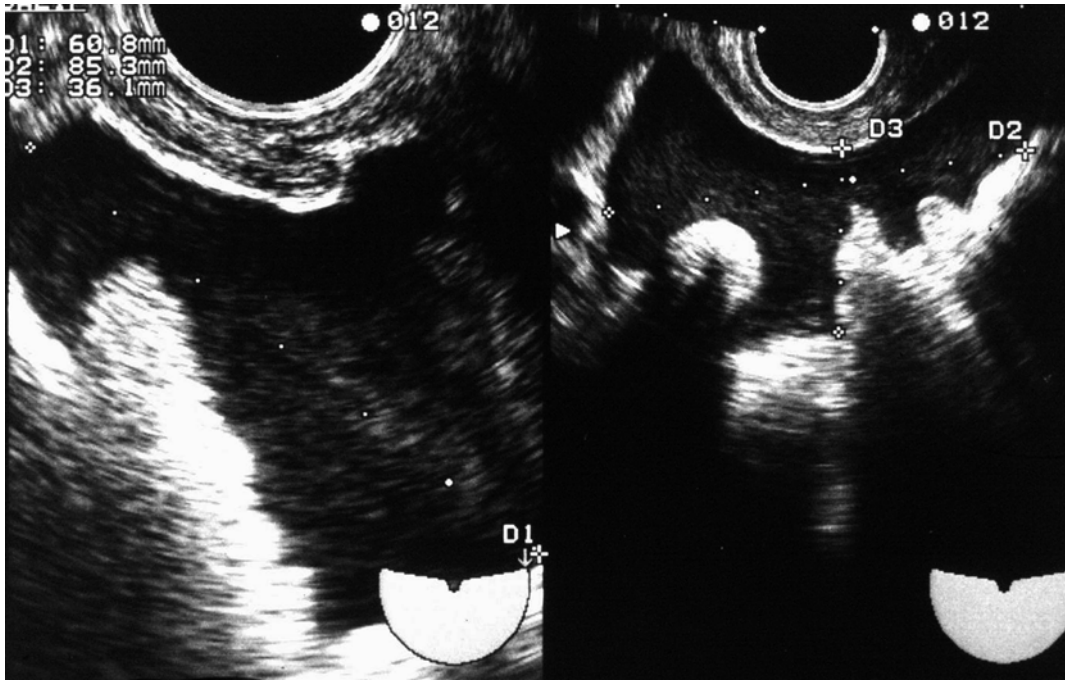

Fig. 16.10 "Tubal ring" consistent with an ectopic pregnancy in a patient with a hCG = 78 mIU/mL

Spontaneous Resolution of Pregnancy

The use of ultrasound for initial patient evaluation can result in identifying adnexal masses that are highly suggestive of an EP, in association with hCG levels that are below the threshold level (Fig. 16.11). Clinicians often feel obligated to treat patients for fear of rupture of an EP. Frates et al. determined that, regardless of the four adnexal findings noted in the prior section, there was no significant difference in rate of tubal rupture, which ranged from 17.6 to 28.4 % [17]. They found the most sensitive ultrasound finding of rupture was a moderate to large amount of free fluid. Thus, in a hemodynamically stable patient, there is no need for urgent intervention if there is either no or only a small amount of fluid in the cul-de-sac or abdomen. Korhonen et al. observed patients who had decreasing or stable hCG levels, an adnexal mass less than 4 cm in size, and no embryonic cardiac activity [24]. They found the rate of spontaneous resolution of a suspected or definite EP was 88 % when the initial hCG was less than 200 mIU/mL, and 25 % when the initial hCG was over 2000 mIU/mL. It must be emphasized that the hCG levels were stable or decreasing in these patients. However, this study demonstrated that observation is a reasonable option in well-selected patients, meeting criteria for spontaneous resolution of their EP.

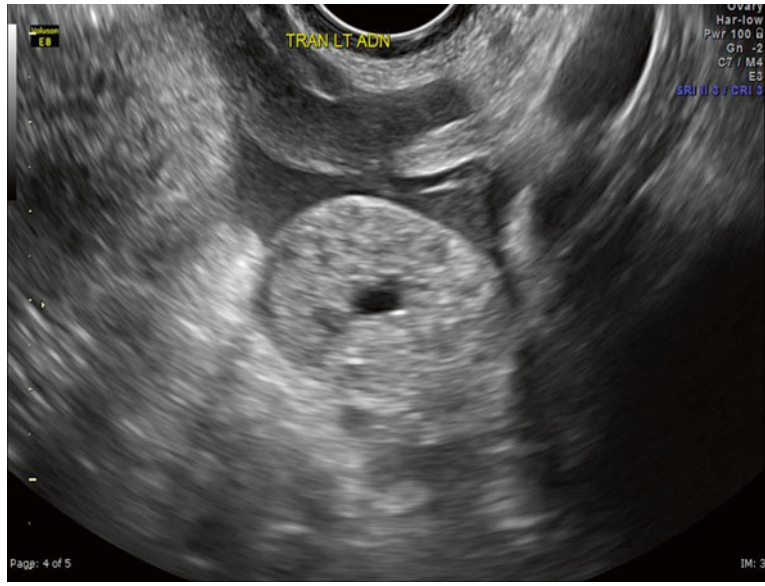

Fig. 16.11 Significant hemoperitoneum identified in a patient with a hCG = 465 mIU/mL

Unusual Ectopic Pregnancies

Heterotopic Pregnancy

The presence of an EP in combination with an IUP is designated a heterotopic pregnancy (Fig. 16.12). The rate of such pregnancies with spontaneous conception may be as low as 1 in 30,000. However, the increased use of assisted reproductive technology has led to an increased incidence of heterotopic pregnancy, perhaps as high as 1 in 110 [25, 26]. One must establish a routine of performing a thorough evaluation of all patients to avoid missing a concomitant EP when a definite IUP is identified.

Interstitial Pregnancy

Interstitial pregnancies are those pregnancies located within the interstitial portion of the fallopian tube and lateral to the endometrial cavity (Fig. 16.13). Three-dimensional (3D) multiplaner reconstruction is incredibly valuable in localizing such pregnancies in the coronal plane. These pregnancies are defined by the ultrasound findings of an empty uterine cavity, a chorionic sac >1 cm from the lateral edge of the uterine cavity (the endometrium), with a thin (<5 mm) layer of myometrium surrounding the chorionic sac [27]. Such pregnancies have also been erroneously called cornual pregnancies. Technically, a cornual pregnancy refers to the implantation of an IUP in one of the cornua of a bicornuate, septate, or subseptate uterus [28]. Angular pregnancies refer to eccentric implantation of an IUP in the cornual area of a normally shaped uterus. Specific criteria for diagnosing an angular pregnancy were offered by Jansen and Elliott in 1981 [29]. These include the following:

- Painful asymmetric uterine enlargement, followed by abortion or vaginal delivery
- Directly observed lateral distension of the uterus, with or without rupture, accompanied by displacement of the round ligament reflection laterally;
- Retention of the placenta in the uterine angle.

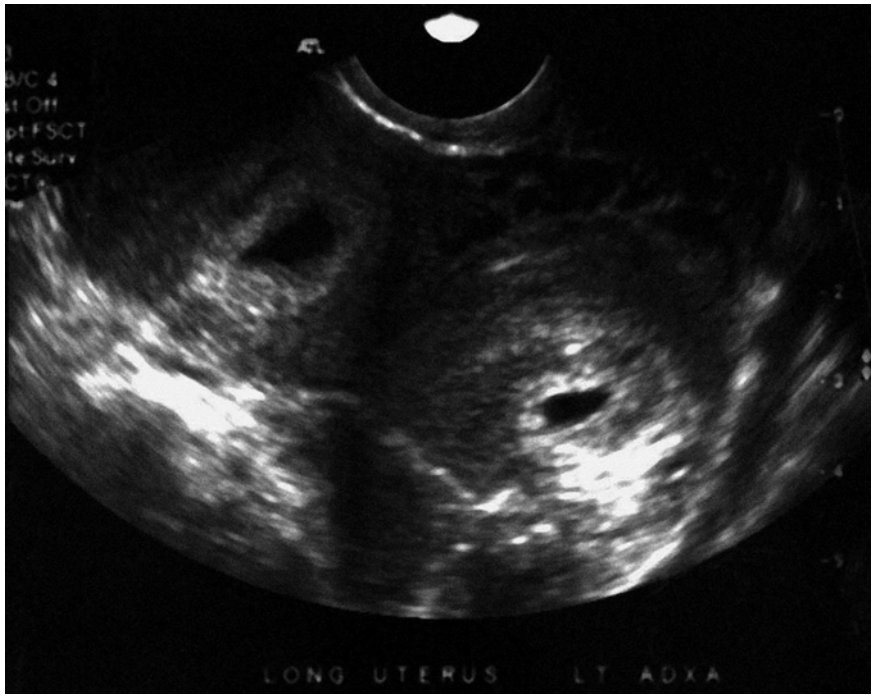

Fig. 16.12 Heterotopic pregnancy with both an intrauterine pregnancy and a tubal pregnancy

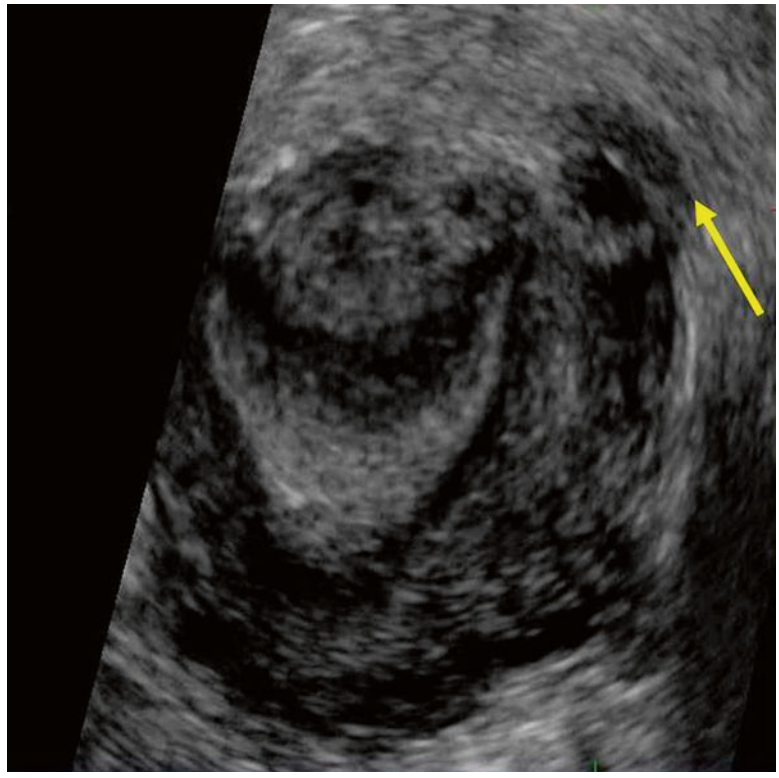

Fig. 16.13 Interstitial pregnancy identified on the 3D coronal view

Angular pregnancies may carry to term, or at least viability, with more conservative management options available. In general, for all of these eccentrically located pregnancies, TVS, particularly 3D with its coronal views, has remarkably changed and clarified their diagnosis. 3D offers the ability to detect uterine anomalies and define the specific implantation site of a pregnancy. Thus, diagnostic criteria are now based on ultrasound rather than surgical pathology. Correct designation is imperative for proper communication of the ultrasound findings.

Ovarian Pregnancy

Ovarian pregnancies are rare with 0.15–3 % of EP occurring in the ovary [30, 31]. The diagnosis includes an empty uterine cavity with a gestational sac, yolk sac, fetal cardiac activity, or embryo visualized in the ovary [32] (Fig. 16.14). The ultrasound criteria for diagnosing an ovarian EP are (1) a wide echogenic ring with an internal echolucent area and (2) a yolk sac or fetal heart motion in the ovary [32]. The diagnosis is confirmed histologically by the Spiegelberg criteria which follow [33]:

- The gestation occupies a normal position of the ovary,
- The gestational sac, thus the ovary, must be attached to the uterus by the ovarian ligament,
- Ovarian tissue is histologically proven in the wall of the gestational sac, and
- The fallopian tube on the affected side must be intact.

Abdominal Pregnancy

Abdominal pregnancies are quite rare. However, there is significant maternal and perinatal mortality and morbidity encountered with such pregnancies. This is due to implantation that occurs outside of the uterus, anywhere in the abdomen. Mortality is markedly higher when attachment occurs to the liver or spleen [34]. The diagnosis is often made later in pregnancy, as the pregnancy

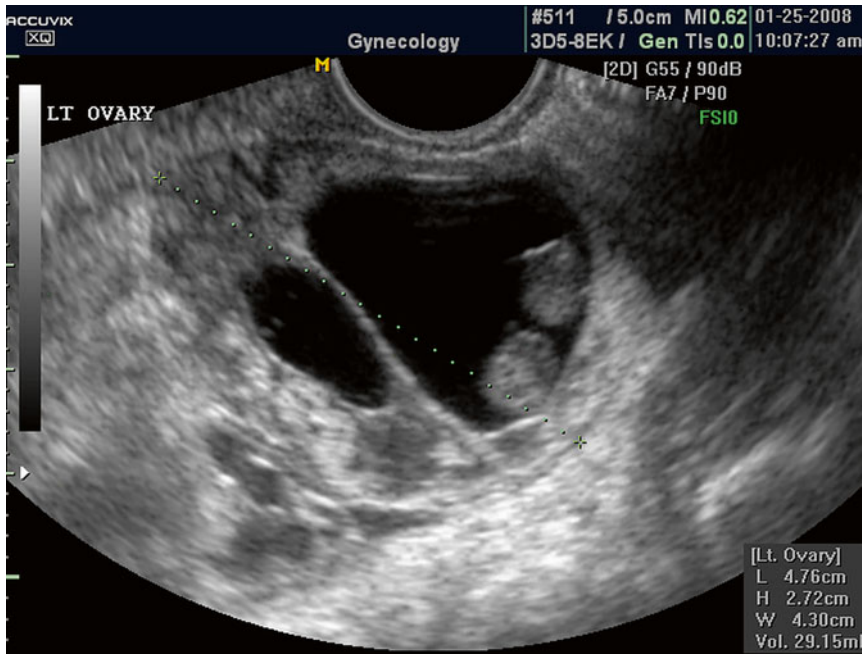

Fig. 16.14 Ovarian pregnancy with nonviable embryo identified in a gestational sac within the ovary

has the ability to expand in the abdomen. Studdiford's criteria for appropriate diagnosis include the following [35]:

- The fallopian tubes and ovaries are normal,
- There is no abnormal connection, e.g., fistula, between the uterus and the abdominal cavity, and
- The pregnancy is related solely to the peritoneal surface without sings of prior tubal rupture.

Diagnosis requires demonstration of an empty uterus, often normal in appearance, with the fetus contained within a gestational sac that is separate from the uterus and cervix [36] (Fig. 16.15).

Cervical Pregnancy

Cervical pregnancy has an incidence of 1:1000–1:16,000 [37]. Diagnosis requires the demonstration of a gestational sac with a yolk sac or embryo in the endocervix, with an "empty" uterine cavity (Fig. 16.16). If the pregnancy implants higher, near the uterine cavity, it is called a cervicoisthmic pregnancy [38]. Previously, diagnosis of a cervical pregnancy was confirmed histologically with Rubin's criteria applied to the surgical specimen. These criteria include [39]:

- Cervical glands are opposite the trophoblastic tissue,
- The trophoblastic attachment is below the entrance of the uterine vessels to the uterus or the anterior peritoneal reflection, and
- Fetal elements are absent from the uterine corpus.

Current treatment is more conservative often with direct injection of methotrexate or potassium chloride (KCl), uterine artery embolization, or more conservative surgical approaches [37]. Thus, Rubin's criteria cannot be applied to pregnancies treated without hysterectomy.

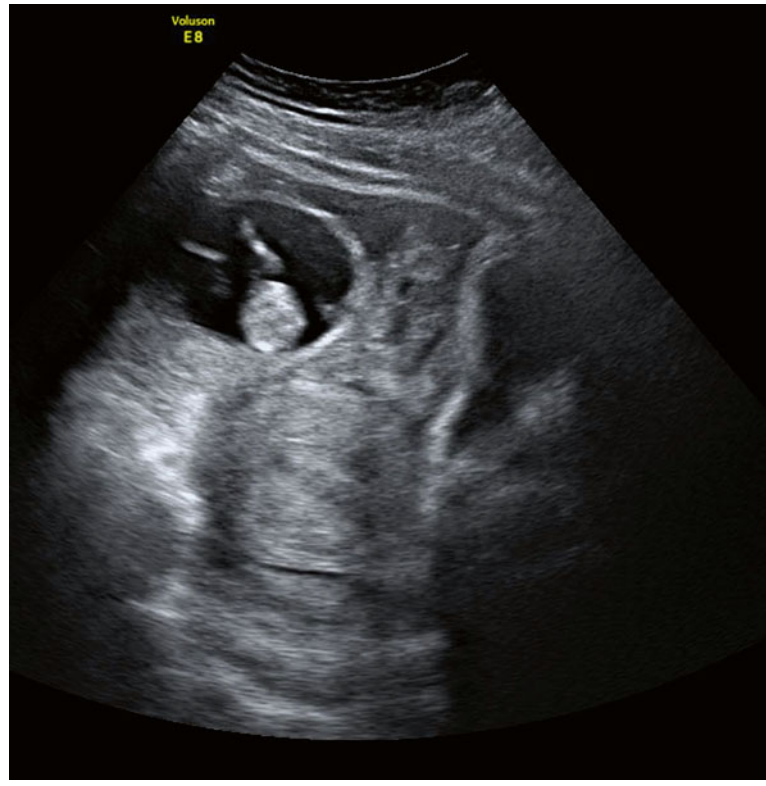

Fig. 16.15 Abdominal pregnancy on transabdominal ultrasound. Note the "empty" uterus

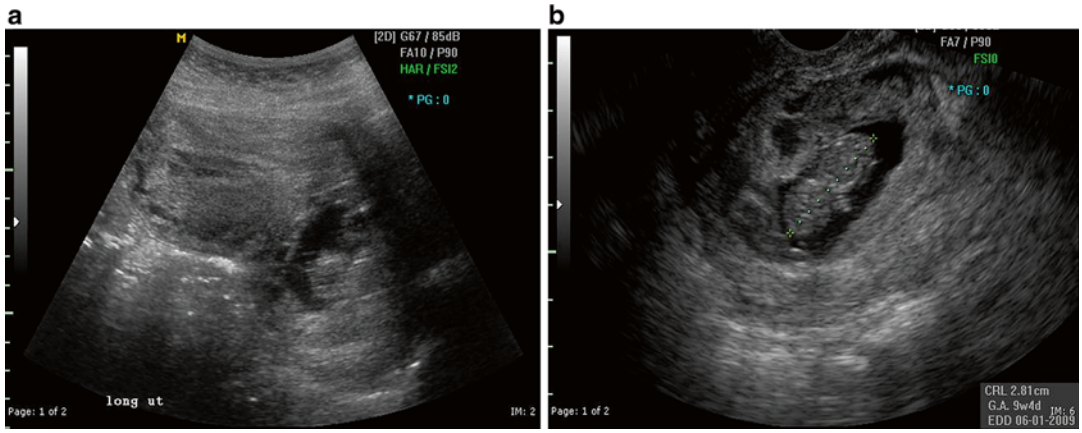

Fig. 16.16 (**a**, **b**) Cervical pregnancy with an embryo visualized in the endocervix

Cesarean Scar Pregnancies

These pregnancies are increasing in frequency. Timor-Tritsch and Monteagudo published an extensive literature review in 2012 regarding this topic [40], which will be reviewed in a subsequent chapter (see Chap. 17).

Summary

Ectopic pregnancy remains a challenging and critical diagnosis, as conservative medical and surgical treatment options rely on early diagnosis. Ultrasound remains the mainstay in diagnosis in coordination with other laboratory tests, particularly quantitative hCG and, in select patients, serum progesterone. Clinical care algorithms are appropriate when ultrasound fails to determine the pregnancy location, the so-called pregnancy of unknown location. In hemodynamically stable patients, such algorithms allow appropriate follow-up until one determines the pregnancy location and its viability status. An established examination protocol is crucial in evaluating patients with suspected ectopic pregnancy, to assure proper diagnosis of pregnancies that are implanted in unusual locations. Strict adherence to such protocols and algorithms allows timely and accurate diagnosis, with appropriate and patient specific treatment options.

Teaching Points

- Patients with pregnancies of unknown location who are hemodynamically stable can be managed expectantly as most are ultimately diagnosed as a viable or failed intrauterine pregnancy.
- A thin endometrium, ≤8 mm, is associated with an abnormal pregnancy in 97 % of patients whose hCG is below the discriminatory level.
- In early pregnancy, a cystic structure within the endometrium, in the absence of an adnexal mass is associated with an intrauterine pregnancy in >99 % of patients.
- A yolk sac or embryo with or without a heartbeat in the adnexa is diagnostic of an ectopic pregnancy
- Ultrasound can be justified prior to obtaining a quantitative hCG, as 50 % of ruptured ectopic pregnancies have hCG levels <1000 mIU/mL.
- Observation is appropriate in hemodynamically stable patients, as spontaneous resolution of ectopic pregnancy occurs in 25–88 % of patients.
- There are specific criteria for diagnosis of ectopic pregnancies in unusual locations.

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A Consequence of Cesarean Delivery: First-Trimester Cesarean Scar Pregnancy

17

Ilan E. Timor-Tritsch, Ana Monteagudo, and Terri-Ann Bennett

Introduction/Terminology

Before discussing epidemiology, the diagnostic issues and management of cesarean scar pregnancy (CSP) are important to touch upon. There are various terms and names used to define this entity and special form of early pregnancy which is often referred to as "cesarean ectopic pregnancy," "cesarean scar ectopic," or "cesarean delivery scar pregnancy." Other terms may also include the word "ectopic." Since the majority of reports use what we think is the correct and most fitting term for the disease, we have used "cesarean scar pregnancy" (in short CSP) in all of our writings. We, therefore, are consistent in this chapter, too.

In fact there are three main reasons to avoid using the term "ectopic." First, CSP is *well within the uterine cavity*. The placenta at times (but not always) is squeezed into the niche or dehiscence created by the cesarean delivery in the lower segment of the uterus or at the level of the internal os. If untreated, the gestational sac and the embryo/fetus will develop within the uterine cavity. Second, a CSP can lead to a live offspring as opposed to any kind of true ectopic pregnancy that rarely, if ever, results in a viable neonate. Last, treatments devised for true ectopic pregnancies and applied for a CSP may not work or may even cause complications.

Our analysis of 751 cases of CSP reviewed until 2012, found that almost a third (30 %) were misdiagnosed or diagnosed at a late gestational age, significantly contributing to a large number of treatment complications that could have been avoided by an early and correct diagnosis. Although an exact number cannot be quoted, it seems that, due to a higher awareness of the disease, among 1223 cases found in the literature published between 2012 and 2014, the number of misdiagnoses appeared to have dropped significantly.

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Background

Due to the close and causal relationship between a previous CD and CSP we have to discuss the gradual but steady increasing rate of CD in the USA and the rest of the world. In the USA the rate of CD slowly increased from 5 % in 1970 to 32.9 % in 2009 [1]. Recent national statistics by the Centers for Disease Control and Prevention report a leveling off of CD rate, which in 2012 reached 32.8 % [2]. Rates ranging from 35 to 80 % were reported in other parts of the world [3], leading us to believe that the incidence of CSP is higher in those countries than in the USA.

Keeping in mind the causative connection between CD and its recognized consequences, such as the placenta previa and morbidly adherent placenta (MAP, placenta accreta and percreta) in the last decade, many Ob/Gyn practitioners became increasingly exposed to the clinical picture of MAP. Most have rarely, if ever, faced a patient with a first- or early second-trimester CSP. The learning process was traumatic resulting in misdiagnosed patients with CSP as "aborting gestations," "ectopic pregnancies," and "cervical pregnancies." Also, obstetricians were confronted with diagnostic and management dilemmas. When "traditional" treatments, such as D&C and systemic methotrexate (MTX) were employed, practitioners experienced severe and almost unmanageable vaginal bleeding that, at times, led to hysterectomy. If "low lying" pregnancies were left to continue, many resulted in second trimester uterine ruptures and profuse internal or vaginal bleeding causing loss of the pregnancy and requiring hysterectomy. Even in reviewing the literature, one could usually find reports of single or sporadic cases or a series of one to two dozen cases that would fit the clinical picture. It is clear, that it was impossible to learn from the numerous, previously used treatments, "tested" on few patients (sometimes only one). The published review compiling 751 patients diagnosed with CSP [4] may have helped to shed light on the various treatments and their complications; however, to date, there is no universally recognized treatment protocol adopted by professional societies. Our chapter will discuss the pathogenesis, diagnosis, counseling and management options to treat CSP based upon evidence in the literature as well as our own clinical experience.

What Is a Cesarean Scar Pregnancy?

Cesarean scar pregnancy develops if a blastocyst implants *on* the uterine scar or *in* the dehiscence (otherwise known as a "niche") resulting from repair of the uterine incision at the previous CD. Implantation of the fertilized oocyte in the faulty anterior uterine wall will give rise to the CSP.

Before engaging in the diagnosis of CSP we will devote a paragraph to discuss the two ways an incision made at the time of the CD heals and appears after it was repaired. Normally we expect that healing tissues generate a thick scar without leaving behind a defect. At times, a dehiscence or as it is usually referred a niche, with a certain depth and width marks the area of the previous CD and can be seen with or without a saline infusion sonohysterography [5]. The niche can be triangular or rectangular and can be filled with fluid (Fig. 17.1a). The size of the niche on a sagittal section of the uterus may be misleading; therefore, the area should always be looked at in the transverse plane on which the real size of the dehiscence can be appreciated (see Fig. 17.1b). This is logical, since most primary Cesarean incisions are performed from side-to-side, e.g., in the transverse plane. Bij deVaate et al. [6] published an extensive review analyzing 21 articles dealing with the prevalence, potential risk factors for development and symptoms related to the presence of uterine niches following CD. The prevalence of a niche after a CD was found to vary between 56 and 84 %. Several risk factors for development of niches were found: the technique of repair, location of the incision, wound healing, and probably the number of layers included in the closure as well as multiple CDs and uterine retroflexion. The dehiscence left behind by the previous CD may be extensive and reaches the anterior uterine wall or the area below the bladder in the shape of a fistulous connection between the uterine cavity and the abovementioned areas (see Fig. 17.1c, d).

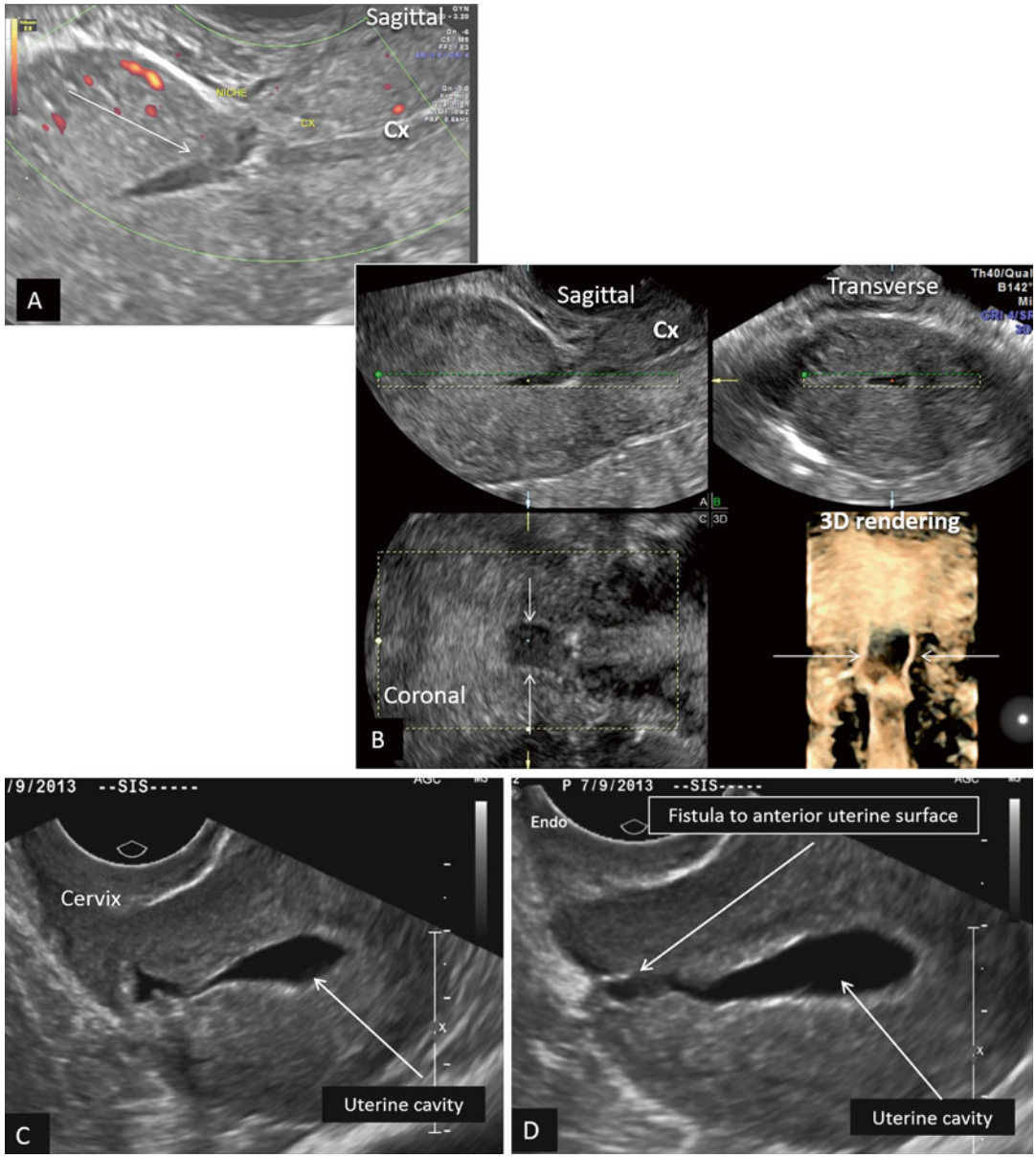

Fig. 17.1 Niche/defect left behind by the previous CD. (**a**) Sagittal image of the niche marked by an *arrow* (*Cx* cervix). (**b**) Three-dimensional orthogonal images of the uterus showing the niche (*arrows*). The width of the dehiscence should always be looked at on a transverse or coronal view since that is the real size of it. Unenhanced images. (**c**, **d**) At times, the niche/dehiscence extends all the way from the uterine cavity to the anterior surface of the uterus. Saline infusion sonographic images

At times, the niche is deep and wide (Fig. 17.2a), explaining the deep insertion of the tiny placenta with its rich blood supply (see Fig. 17.2b, c). Since the prevalence of niches is relatively high, it can be expected that the possibility of such deep implantation is realistic; therefore, a careful scrutiny of the small placenta and its vessels should be performed in all first-trimester diagnoses of CSP.

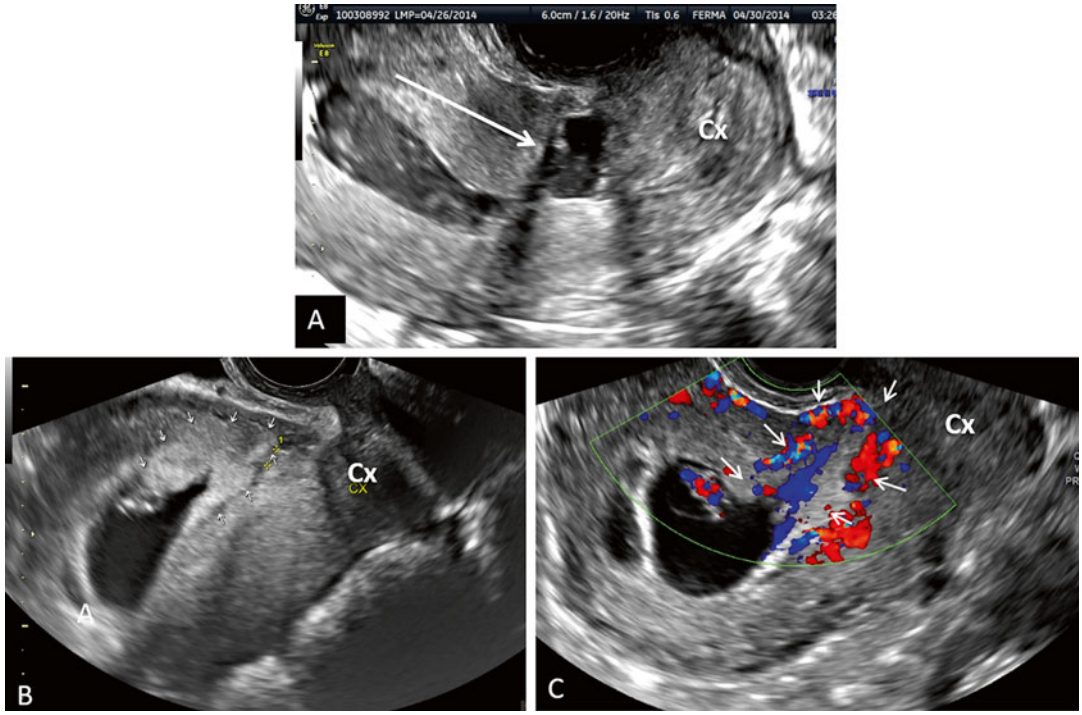

Fig. 17.2 Placental implantation into the niche of a previous CD. Sagittal images (*Cx* cervix). (**a**) Saline infusion sonohysterography of a uterus with a large niche. (**b**) Gray scale sagittal image of a CSP. Note the implantation of the placenta in the niche outlined by *small arrows*. (**c**) Color Doppler image of the same CSP demonstrating the invasion of the placenta (*outlined* by *small arrows*) with its blood vessels into the myometrium

Incidence/Risk Factor

Estimated incidence rates of CSP range between 1/1800 and 1/2500 of all CDs performed [7–10]. Seow et al. [11] states that CSP was seen in 0.15 % of all pregnancies with a history of a previous CD. The above numbers appear unrealistic; however, their true incidence is unknown due to the lack of population based statistics (registries).

The only risk factor for CSP is a previous CD. However, since we found about eight cases of recurrent CSP in the literature, including our own case with four recurrences [12], we have to consider a previous CSP as a rare but possible risk factor for this entity.

Pathogenesis of CSP

Later in this chapter, we will provide evidence that the histology of the tiny placental insertion or myometrial invasion of a CSP in the first trimester of the gestation is identical with the histologic findings of a MAP in the second and third trimester of pregnancy. The only scientifically proven fact is that, in both diseases (CSP and MAP), intervening fibrinoid layer between the myometrium and the cytotrophoblastic shell in the placenta is naturally present between the endometrium in normally attached placentae when thinned or missing. This fibrin layer (fibrinoid material) is known by the name of Nitabuch layer. Previous uterine surgery or uterine inter-

ventions lead to *thin or absent decidua basalis in scarred areas*, *as well as the abovementioned protective layer* of the lower uterine segment. In CSP and in MAP this membrane is missing and the placental villi attach themselves and penetrate between the myometrial fibers into the depth of the uterine wall.

Other theories, such as the role of a low oxygen tension at the area of the scar providing a stimulus to help the invading cytotrophoblast [13, 14], as well as the in vitro studies of Kliman et al. [15] with trophoblast and EM explants, showing a strong propensity for attaching to exposed extracellular matrix and then to endometrial epithelial cells, are the most frequently quoted. Both theories support the observation that the more CDs a patient has, the higher risk of placenta previa and a MAP.

Diagnosis of CSP

The two diagnostic modalities used are ultrasound and MRI; however, ultrasound is the best modality. Transvaginal sonography (TVS) presents an advantage over transabdominal ultrasound (TAS), since it has a higher resolution and can be placed in close proximity to the low, anterior gestational sac. MRI has been used for imaging and is expensive. In addition, it requires moving the patient to a radiology site. Also, MRI lacks the color Doppler flow that provides a high resolution image, which is important in establishing a correct diagnosis.

The diagnosis of CSP requires a high clinical index of suspicion. We reiterate, that every woman with a history of a previous CD and a positive pregnancy test, presenting in the first trimester of the pregnancy, should be considered a "rule out CSP" until proven otherwise. Stirnemann et al. [16, 17] published studies to lay the basics for such screening if proven significant. Until that time, this should be strongly considered, since there is no downside to that first early scan. Godin et al. [18], Vial et al. [19], and Seow et al. [20] published similar sonographic criteria they used to define a CSP; however, other authors used additional characteristics, relying mostly on single cases.

Our diagnostic criteria of CSP [4, 21] took in consideration a history of previous CD, a positive pregnancy test and the following sonographic criteria (Fig. 17.3):

- Endometrial and endocervical canal devoid of a gestational sac;
- Placenta and/or a gestational sac embedded on or in the hysterotomy scar/niche;
- In early gestations, a triangular gestational sac that fills a niche of the scar (Fig. 17.4);
- Thin or absent myometrial layer between the gestational sac and the bladder;
- The presence of a chorionic sac, with or without embryonic/fetal pole and/or yolk sac and with or without heart activity;
- The presence of a prominent and at times rich vascular pattern at or in the area of a CD scar. As a rule, detection of peri-trophoblastic blood flow, detected by the most sensitive Doppler settings around a low, anteriorly situated chorionic sac, in a patient with a previous CD, is a reliable sign of CSP.
- It is remarkable that, at very early stages of the pregnancy (4–5 weeks), the blood vessels tend to concentrate on the anterior side of the chorionic sac (Fig. 17.5) "marking" the site of the placental implantation.
- The usefulness of 3D ultrasound in the diagnosis is debated. However, it furnishes information regarding the exact location of the sac, its vascularity and volume, the latter two in a quantitative fashion (Fig. 17.6). We use the above measurements to follow the healing process of the treated cases or for the early warning signs of an impending arteriovenous malformation (AVM) developing at the treatment site.

If an AVM was suspected (at times, this may be the presenting sonographic picture), Doppler measurements of the blood velocity were measured and expressed by the peak systolic velocity (PSV) in cm/s. Velocities above 39 cm/s were considered for uterine artery embolization (UAE) by the interventional radiologist. This evaluation

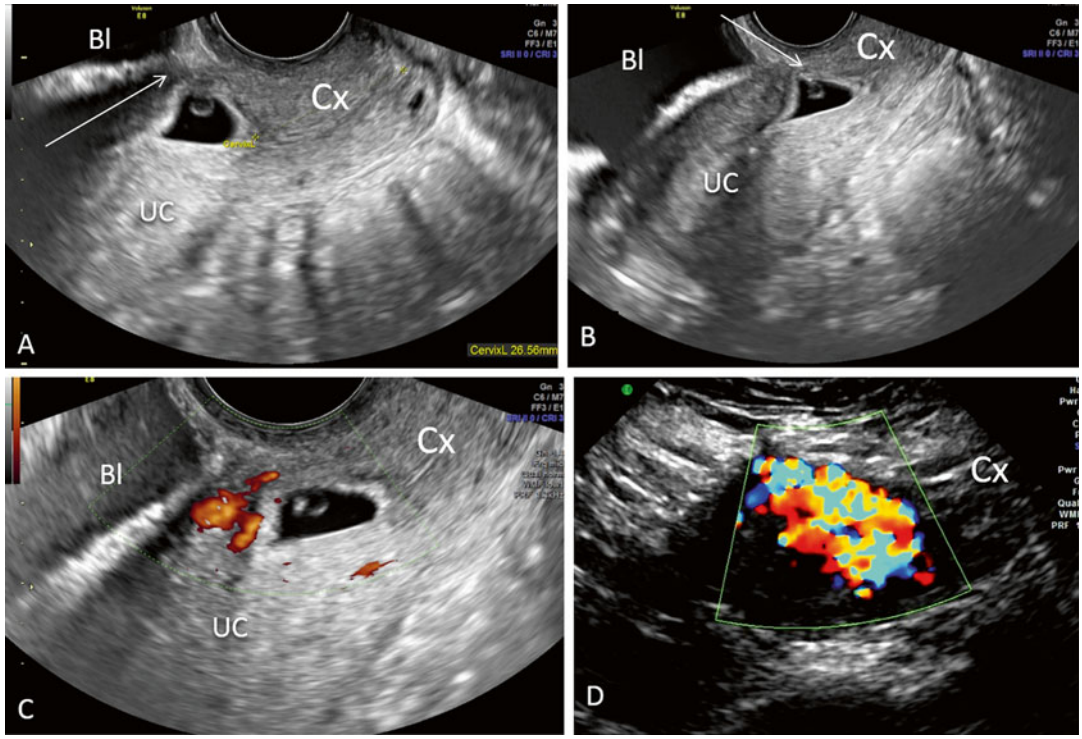

Fig. 17.3 Sonographic markers of CSP (*Cx* cervix, *Bl* bladder, *UC* uterine cavity). (**a**) Empty uterine cavity and cervical canal. Low anterior triangular gestational sac with yolk sac in close proximity to the bladder (*long arrow*). (**b**) Triangular gestational sac with close proximity to the bladder. (**c**) The developing vascularity between the sac and the bladder. (**d**) Arteriovenous malformation in a CSP that required UAE

is best done when the region of interest of the Doppler interrogation is constricted to the questionable area, using the appropriate pulse repetition frequency and filter settings.

These are pathological, high velocity, low resistance "short circuits" of the blood stream between an organ's arterial and venous supply. Ultrasound presents a valuable tool for the diagnosis of AVM and guideline for their treatment [22]. Although uncommon, they may cause dangerous hemorrhages due to disrupted blood vessels, after miscarriage or uterine instrumentation [23]. The acquired form, seen in CSP, is usually traumatic, resulting from prior dilation and curettage (D&C), therapeutic abortion, uterine surgery, or direct uterine trauma. Their incidence is about 1 % of CSPs. In our series of 60 CSPs five, patients had AVM [24].

Differential Diagnosis of CSP

There are two main differential diagnostic entities to consider: First, a *cervical pregnancy*, which is rare and has no history of prior CDs. Second, a *miscarriage in progress*, which can be seen in the cervical canal or close to the internal os and "on its way out" having no heart activity. Also, under pressure on the cervix with the vaginal probe, the sac will slide back-and-forth, while a true CSP will stay fixed. It should be noted that misdiagnosis has, at times, severe consequences. The proof is in the literature: 107 of the 751 cases of CSP reviewed (13.6 %) were missed or misdiagnosed leading to complications (e.g., hysterectomy and loss of fertility) [4]. Figure 17.7 demonstrates a simple method to distinguish between the two,

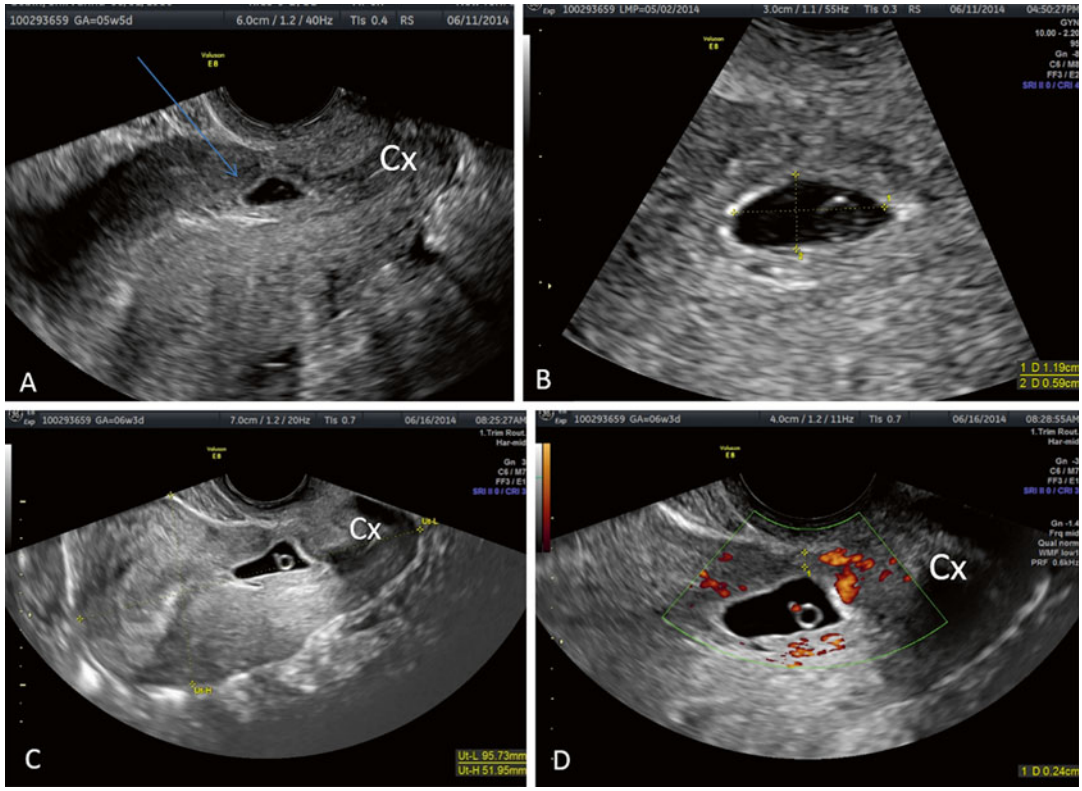

Fig. 17.4 Additional images of the shape of the early 4–6 week chorionic sac of the CSP (*Cx* cervix). (**a**) Flat sac. (**b**) Oval sac. (**c**) Triangular sac. (**d**) Square sac

abovementioned, differential diagnostic entities and a true CSP.

However, it is extremely important to realize that this simplified diagnostic aid is valid and reliable only while the gestational sac is small (e.g., 5–6 mm in diameter or 5–6 postmenstrual weeks) and remains "local," close to the niche or above the scar. In other words, the sac did not start to elongate and move/expand cranially to fill the uterine cavity. In this case, the sac will be found increasingly in the uterine cavity misleading the uninitiated observer to think that it is an intrauterine sac. In such cases one should shift the attention from the sac and concentrate upon the blood vessels of the tiny placenta, which stay in their original site of implantation, thereby holding the most important diagnostic feature of CSP: the true site of placental implantation. Figures 17.2, 17.3, 17.4, and 17.5 clearly demonstrate the abovementioned diagnostic principle.

Lately, clinicians and clinical researchers have started to pay attention to the exact location of placental implantation in the area of the scar/niche left behind by the previous CD. Vial et al. [19] suggested that there are two kinds of CSPs, based on depth of implantation. The question is whether a deeply implanted chorionic sac *in* a niche or dehiscence, close to the bladder with very thin or no visible myometrium (Fig. 17.8a, b) will result in a worse outcome than if inserted *on* top of a scar that has some thickness (see Fig. 17.8c, d). Comstock et al. [25] and personal communication with Cali G. refer to "on-the-scar implantations" as "low lying sacs" and assume that these are the CSPs that may proceed to third trimester giving rise to MAP. Deeply implanted in the niche, surrounded by myometrium and seldom reach term is a "true" scar pregnancy. We slightly differ about the latter form of CSP since we have witnessed the reaching delivery of a live offspring.

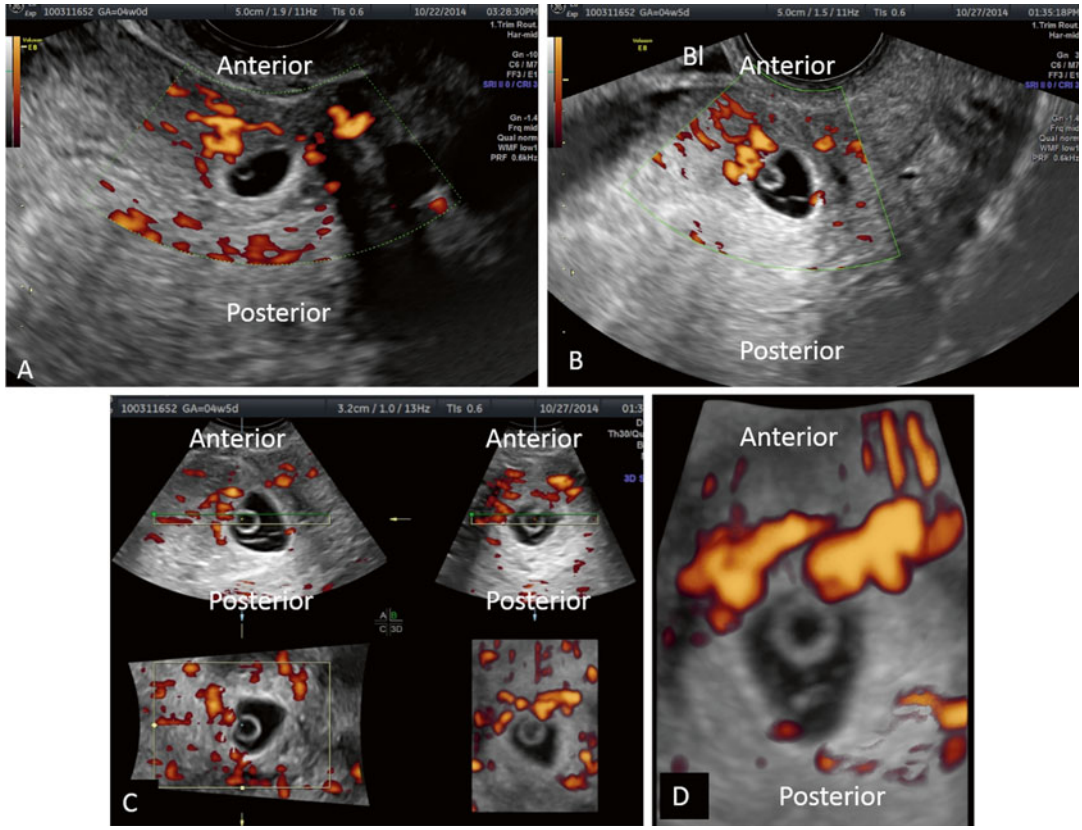

Fig. 17.5 The developing vascular grid of the early CSP. (**a**, **b**) 2D color Doppler of the vessels surrounding the chorionic sac. (**c**) Three-dimensional, orthogonal planes and 3D rendering (*lower right picture*) of the vascularity that starts to concentrate on the anterior side of the sac, the future site of the placenta. We suspect that the future placenta will invade the myometrium in the anterior direction. (**d**) Thick-slice 3D rendering of the sac with its vessels clearly more prominent anteriorly

Rac et al. [26] studied 39 patients, of which 14 had histologically confirmed MAP. The smallest myometrial thickness measurement was one of the variables associated with invasion. More research is needed before the gestational-sac-to-bladder distance (see Fig. 17.8) can become useful in counseling patients with CSP in the first trimester of pregnancy.

The Connection Between CSP and MAP

The connection or continuity between CSP and MAP has gradually become evident through clinical observation [27, 28]. We studied placental implantation in the early (second trimester) placenta accreta and in CSP, to find out if they represent different stages in the disease continuum leading to morbidly adherent placenta in the third trimester [29]. Two pathologists, blinded to the diagnosis, evaluated their histologic slides on the basis of these microscopic slides. They could not tell the difference between the two clinical entities and found that both had one thing in common: neither had intervening deciduas between the villi and the myometrium, consistent with the classic definition of morbidly adherent placenta. Therefore, our conclusion is that CSP and an early second trimester placenta accreta are histopathologically identical and represent different stages in the disease continuum leading to MAP in the third trimester.

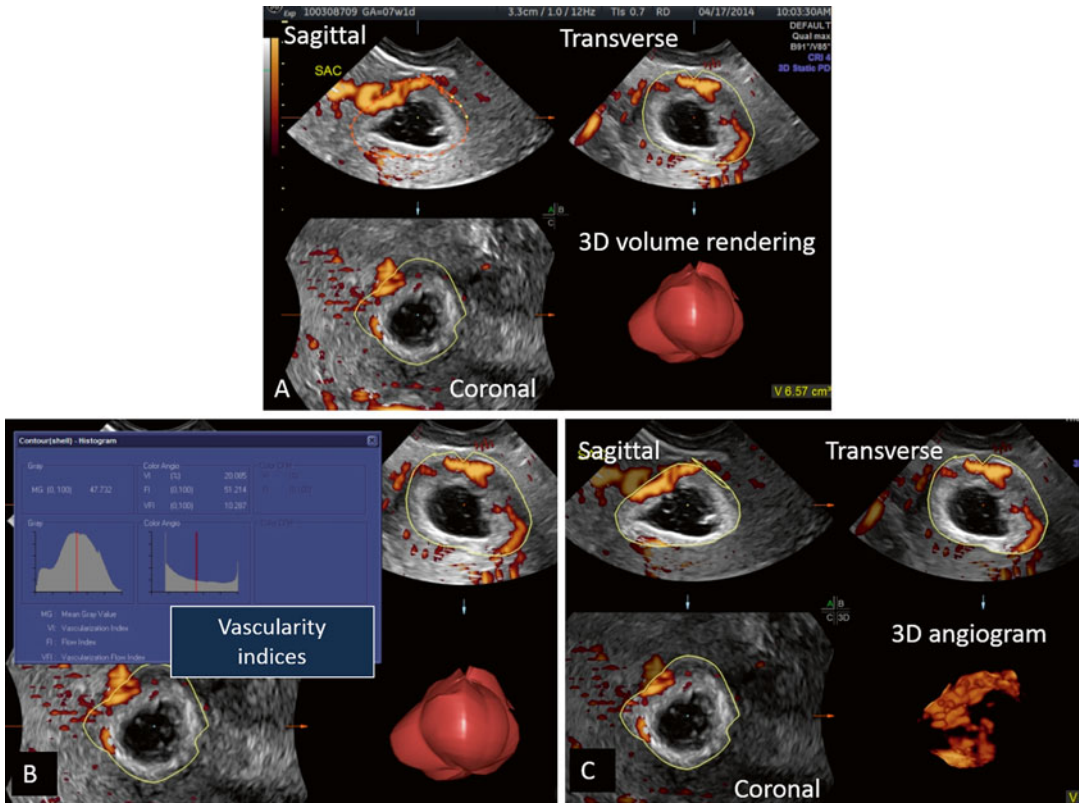

Fig. 17.6 The use of 3D ultrasound in the diagnosis and follow-up of treatment of CSP. (**a**) 3D orthogonal planes with power Doppler used in segmentation (marking the perimeter of the sac) to obtain the volume of it. (**b**) After the volume of the sac is obtained a special algorithm is applied to compute and display the quantitative vessel content of the above volume. (**c**) Visual display of the 3D vascular angiogram that can be used qualitatively for follow-up purposes after local injection of UAE treatments

The next logical question is whether, left untreated, a CSP would result in a live born offspring. We followed ten patients diagnosed with CSPs who opted to continue the pregnancy declining early termination [30]. The diagnosis of CSP was made before 10 weeks. All ten had sonographic signs of MAP by the second trimester. Nine of the ten patients delivered live born neonates, between 32 and 37 weeks. One patient had progressive intractable vaginal bleeding, leading to hysterectomy, at 20 weeks. The other nine patients underwent hysterectomy at the CD. Blood loss ranged from 300 to 6000 mL. Histopathological diagnoses of all placentae was: placenta percreta.

Above, we provided reliable data regarding two clinical issues: (1) CSP is a precursor of MAP, both sharing the same histopathology and (2) pregnancies diagnosed as CSP in the first trimester may proceed to deliver live offspring, risking premature delivery and loss of uterus and fertility. This data can be used to counsel patients with CSP, to make an evidence-based and informed choice between first-trimester termination of an early pregnancy or continuation, risking premature delivery and loss of uterus and fertility.

Map in the First Trimester

MAP can exist in the first trimester of pregnancy. For beginners, Comstock et al. [25] described seven patients after sonographic examination at 10 weeks or earlier with placenta accreta, increta,

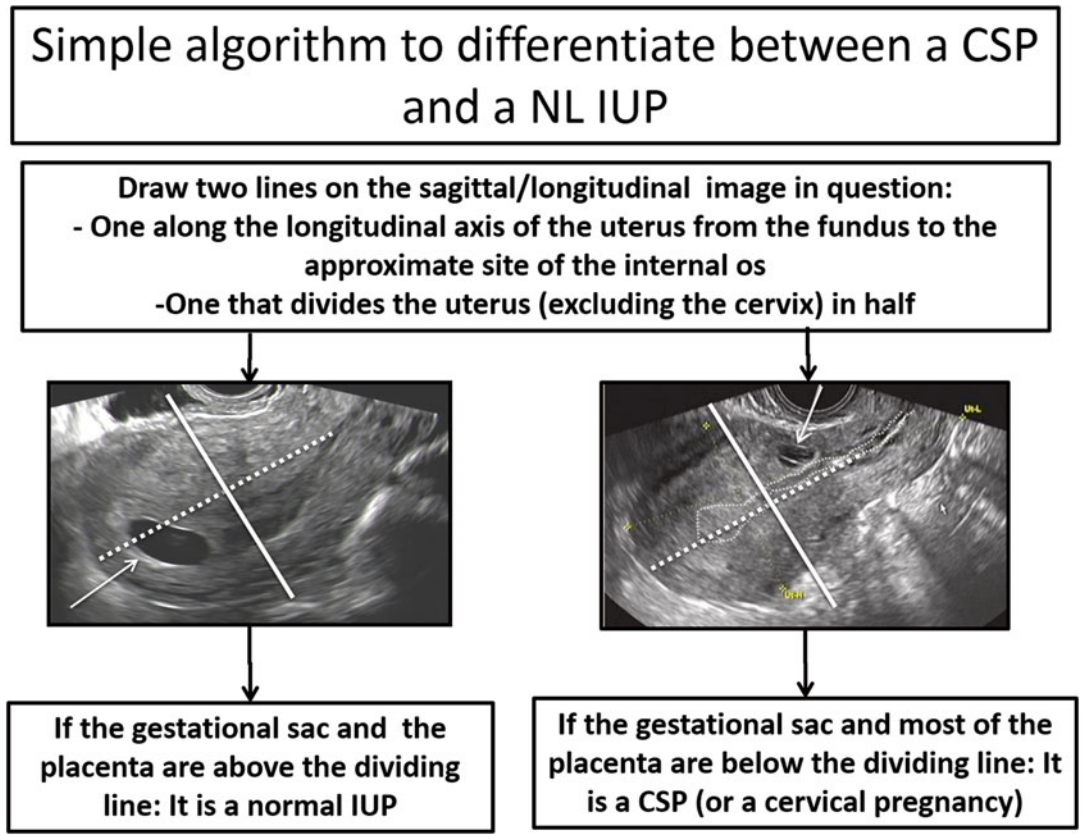

Fig. 17.7 The simple algorithm to differentiate between an IUP and a CSP (or cervical pregnancy)

percreta, not only by their clinical course but, more importantly, by pathologic examination of the uterus. In six, at the time of the early ultrasound, the chorionic sac was located in the lower uterine segment, in the scar area of the previous CD. Two patients underwent D&C, at which time severe bleeding led to hysterectomy. The remaining four had sonographic findings typical of placenta accreta during subsequent scans but delivered at term. The author's conclusion suggested that, in a patient with a previous CD, a chorionic sac detected by a 10 week or less ultrasound, located in the lower uterine segment, suggests the possibility of placenta accreta. A similar article was published by Ballas et al. [27].

Using our material, Fig. 17.9 depicts the early sonographic markers of a MAP: placenta previa, focal loss of the clear space and focally increased vascularity. The patient in this example delivered at 34 weeks and had placenta accreta. In ten patients, we reported [30] the early sonographic markers of MAP could be detected at the end of the first and beginning of the second trimester.

Counseling Patients with a First-Trimester CSP

Prior to treatment and after the reliable diagnosis of CSP, one has to determine if fetal heart beats are seen. If no yolk sac and/or no embryo and/or no heart beats are seen, re-scan every 2–3 days. If, after a week, no heart activity, no yolk sac and/or no embryo are detected, a sonography and biochemistry based follow-up should be planned. Only after this time should the gestation be

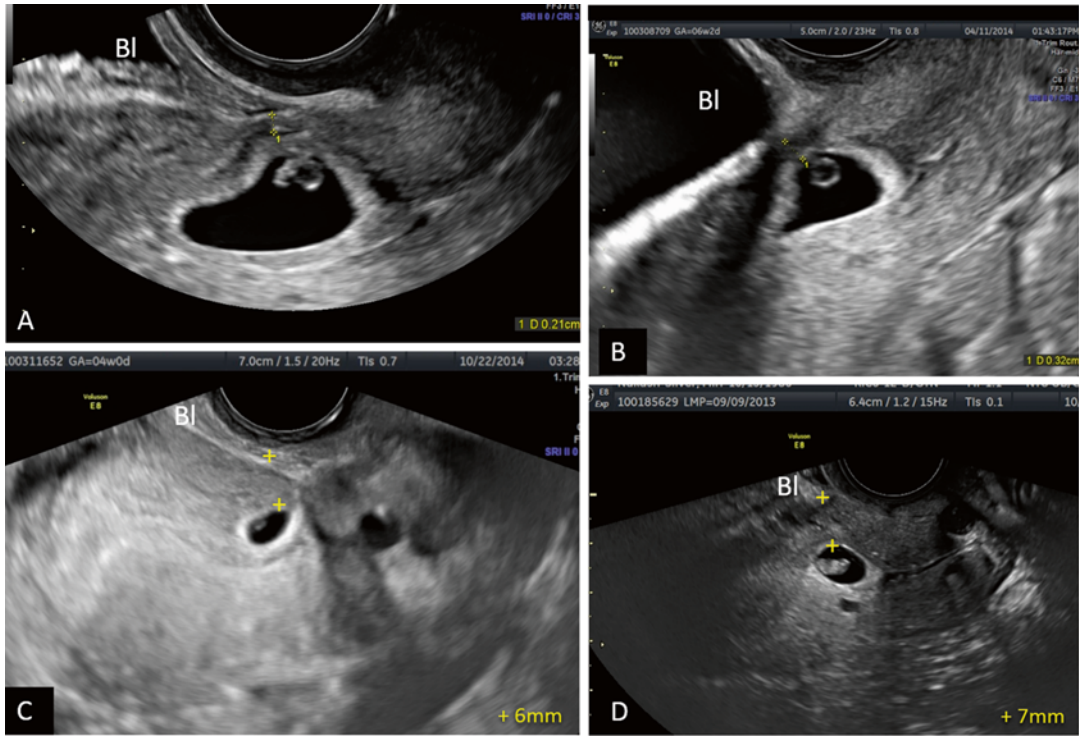

Fig. 17.8 The issue of distance between the anterior uterine surface and the gestational sac: "*in* the niche/scar" or "*on* the scar" (*Bl* bladder). (**a**, **b**) These two are examples of a close proximity of the sac to the bladder (2.1 mm and 3.2 mm, respectively). (**c**, **d**) Depicts two CSPs in which the sac is 6 and 7 mm remote from the bladder

considered live or a pregnancy failure and the serum hCG should be followed until nonpregnant levels are reached. Some management protocols call for systemic administration of MTX, even with the absence of heart beats for early drug effect. While such an approach is not contraindicated, the patient and the provider *must* be sure that under no circumstances is this a wanted pregnancy.

In the case of positive heart activity, counseling should enumerate the two main, clinical management options to reach a decision as early as possible. The two options before further growth of the gestation are: (1) termination or (2) continuation of the pregnancy. Our counseling of patients with a CSP diagnosed in the first trimester of pregnancy underwent a fundamental change. Several years ago we would counsel toward termination of the pregnancy without delay. Recent studies on the natural history of the CSP, with the possibility of reaching term or near term delivery of a live offspring, has changed our counseling. We provide the patient with evidence that this is possible and that the patient should understand that a placenta accreta at the CD may necessitate hysterectomy. Management in the above case should be based on the patient's age, number of previous CDs, desired number of children, and the expertise of the clinicians giving the care. If the patient decides to continue the pregnancy, bleeding precautions should be given. The management should be based upon serial ultrasounds, until a safe gestational age is reached. A multidisciplinary team should be involved in the delivery and blood products should be available, since ultrasound cannot predict the blood loss at surgery. Our general guidelines in counseling and managing the patient with a CSP are shown in Fig. 17.10.

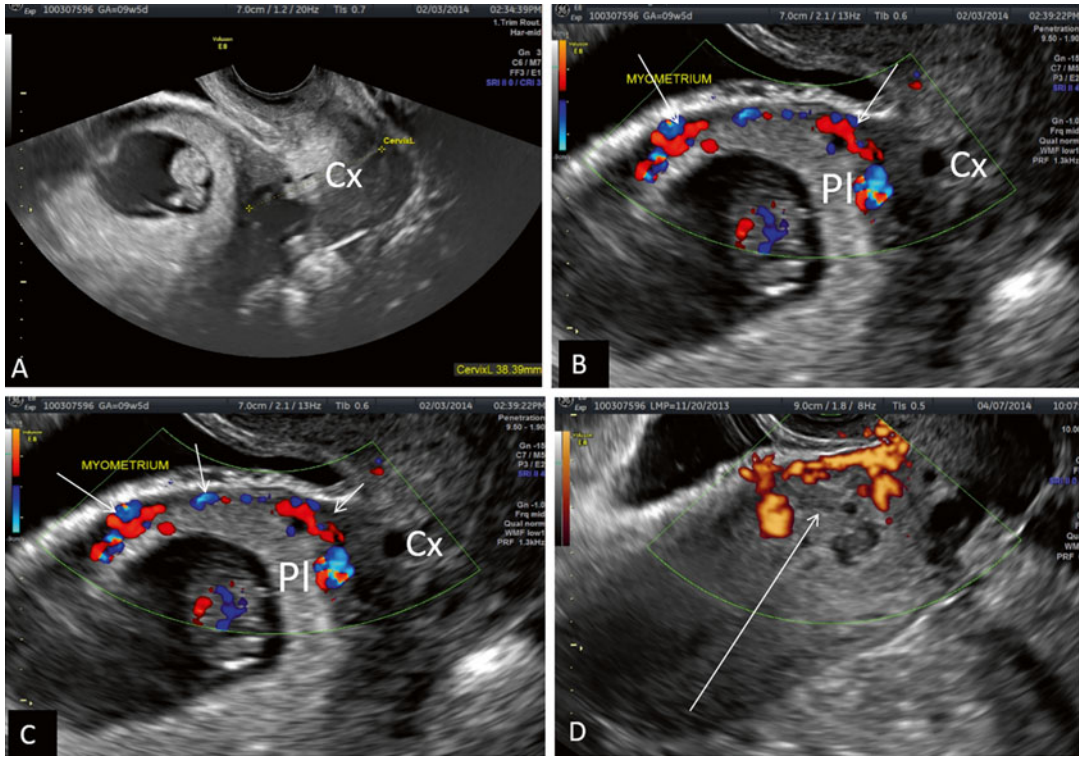

Fig. 17.9 CSP is a precursor of MAP. This is a 9 weeks and 5 days gestation (*Cx* cervix, *Pl* placenta). (**a**) Sagittal, gray scale image of a CSP with an anterior placenta previa. (**b**) Power Doppler reveals two areas of vessel proximity to the bladder with loss of the myometrium (*arrows*). (**c**) Another plane showing the same findings as in (**b**). (**d**) A more lateral section concentrates on an area with clear vessel invasion of the myometrium (*arrow*)

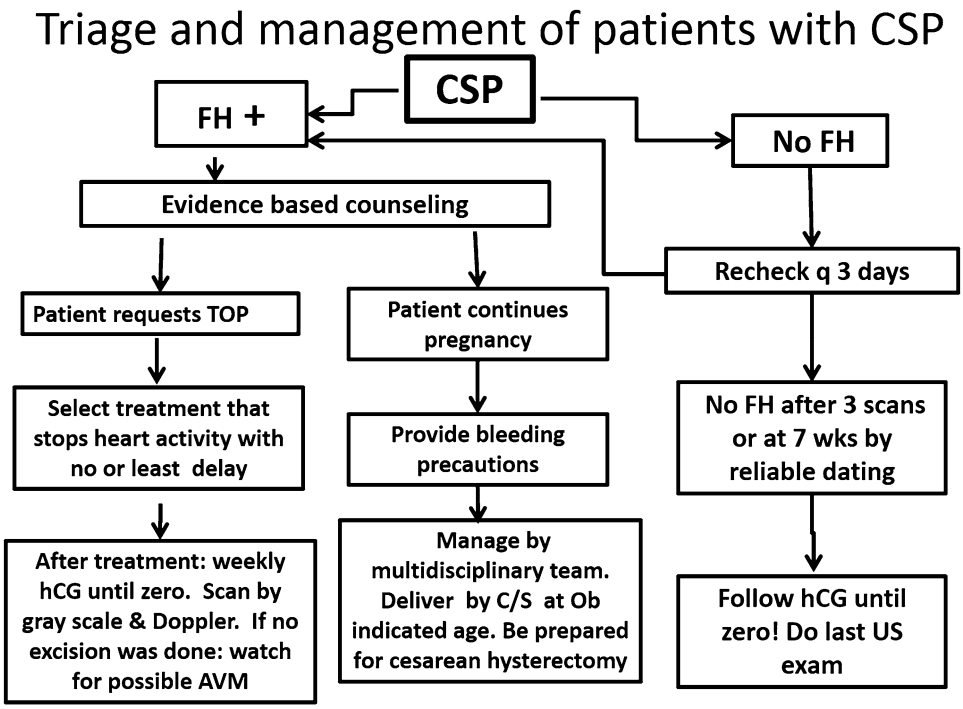

Fig. 17.10 Triage and management of CSP by the presence or absence of cardiac activity

Management of CSP

Treatment regimens and their combinations can be classified as one of the following:

1. Major Surgery (these require general anesthesia)
   (a) Laparotomy (hysterectomy or local excision)
   (b) Excision by laparoscopy, hysteroscopy or by transvaginal surgery
   (c) Dilatation of the cervix and sharp or blunt curetting
   (d) Suction aspiration without dilatation of the cervix
   (e) Excision performed by the vaginal route

   The last two can be guided by continuous, real-time ultrasound.

2. Minimally invasive surgery (does not involve general anesthesia)
   (a) Local injection of MTX or KCl
   (b) Vasopressin locally was also used
3. Systemic medication
   (a) Single or repeated doses of MTX and etoposide (some articles originating from China advocate intravenous use of MTX claiming reasonable success)
   (b) Uterine artery embolization (UAE)
4. Combination of the above treatments. A large number of articles report on combining treatments in a planned, simultaneous or sequential fashion. Treatments are also changed, mostly after the first-line therapy failed. As a matter of fact, it is rare to find a recently (2012–2014) published case or case series in which the patients were managed *only* by one single treatment agent or protocol.
5. Adjuvant measures. Most recently, Foley balloon placement and inflation to prevent and/or control bleeding, following local treatments such as aspiration, curettage and local injection.

It is beneficial for the patient with CSP to be referred to a facility that provides evidence-based care as well as experienced in managing cases, in response to developing emergency situations. Such centers should be able to provide operating rooms, interventional radiology procedures and have available immediately blood transfusion/blood products. The latter, since bleeding complications is typical of this dangerous clinical entity.

Treatment Options Available for CSP

Based upon the in-depth and available literature, analyzing the different aspects of CSP, in 2012 there were about 33 published treatment modalities with their results and complications [4]. No preferred treatment became apparent, however, of the 751 patients D&C (305), surgical excision (laparoscopic, hysteroscopic and transvaginal) (261), UAE (142), MTX (92), and local, intragestational sac injection (86) were the most used.

Between 2012 and 2014, no less than 1223 cases of CSP were published in about 61 peer-reviewed articles. Not surprising is the fact that Chinese authors contributed 91 % of the cases, describing their various and different treatment modalities/combinations of managing approximately 1115 patients. This is due to their large population and over 40 % CD rate. At least 36 primary or combination treatments were found; however, the number is not substantially different from the list of treatment approaches described in our review of 751 cases. No wonder one cannot draw a clear conclusion as to which treatment was the most effective, resulting in the least or no complications. This large number underlines the fact that, in 2015, there is no nationally/internationally agreed upon or suggested management protocol published with a set of guidelines to manage CSP or early first-trimester placenta accreta. While the distribution of the various treatments and their rates of use are found in the tables of our previous review [4], the somewhat different distribution of treatment choices are detailed in Table 17.1.

Despite several treatments for CSP our detailed discussion will be limited to the most used. A much more detailed analysis is found in our in-depth review [4], complete with their efficacy and complication rates. We now add the pertinent data resulting from the review of the 1223 cases published after 2012.

Table 17.1 Treatment options for CSP

Treatments: single or in combination	No. of patients	Percent of 1223 patients (%)
Dilatation and curettage	577	52.4
Uterine artery embolization	309	28.0
Methotrexate	236	21.4
Suction aspiration	81	12.0
Transvaginal excision	119	9.7
Laparoscopic excision	94	7.7
Hysteroscopic excision or guidance	63	5.2
Excision by laparotomy or straight TAH	15	1.2
High-frequency ultrasound	20	1.6

Suction Aspiration or D&C, Alone or in Combination

Based on our first review of treating 305 cases with D&C only or in combination with other means as a "first line" or a backup, therapy had a mean complication rate of about 62 % (range, 29–86 %) [4]. The main complication was unanticipated bleeding, forcing an emergency second or third-line treatment that, almost always, was surgical. At times, hysterectomy became necessary. This option requires general anesthesia.

There were some changes between the results of the two reviews. If D&C was used as a sole treatment, in 69 cases 24 (34.7 %) resulted in complication as opposed to first line or secondary treatment combined with other treatments. Only 52 of 413 (12.2 %) had complications. If UAE was combined with systemic MTX it caused 35 % complications, while combined with other means (e.g., suction evacuation or hysteroscopic excision among others), the rate was only 11.3 %.

As opposed to a spontaneous delivery or spontaneous abortion, where the uterine myometrial grid constricts the bleeding after placental separation, in CSP, the sharp curettage exposes vessels of the gestational sac leading to severe and sometimes unstoppable bleeding since there is less or no adequate muscle grid to contain the bleeding. A sharp curettage might injure the thin myometrium leading to bleeding or even perforation.

If D&C or suction aspiration is still the preferred treatment, blood and blood products as well as a Foley balloon catheter should be readily available [31]. Foley balloon catheters were successfully used to stop and tamponade possible bleeding [32, 33]. Cali et al. [34] successfully used the following sequential treatment approach in eight of their patients. At admission to the hospital, the patient undergoes UAE and, after 5 days, a gentle suction aspiration under continuous, real-time ultrasound is performed by immediate insertion and inflation of a Foley balloon catheter for bleeding prevention and control [31].

A number of recent articles advocate the safe and uncomplicated use of blunt sac aspiration; however, all were followed or preceded by other treatment methods [35]. Interestingly, no complications were seen in 81 suction aspirations in our review of the cases between 2012 and 2014. This probably is attributed to its blunt, as opposed to a sharp curetting at the time of D&C, therefore, less prone to disrupt blood vessels.

Uterine Artery Embolization, Alone or in Combination

This treatment requires general anesthesia. If used as a primary and only treatment, the complication rate among the 64 cases described in the review of 751 cases of CSP was 47 %. It is difficult to evaluate the real complication rates, due to partial or incomplete data in the published articles. In another 78 cases, UAE was used in combination with other treatments. It seems that UAE is not the best first-line treatment, if administered alone as a single agent therapy, since it allows the pregnancy, with its vascularity, to grow and increase. For this reason, Cali et al. [34] delayed

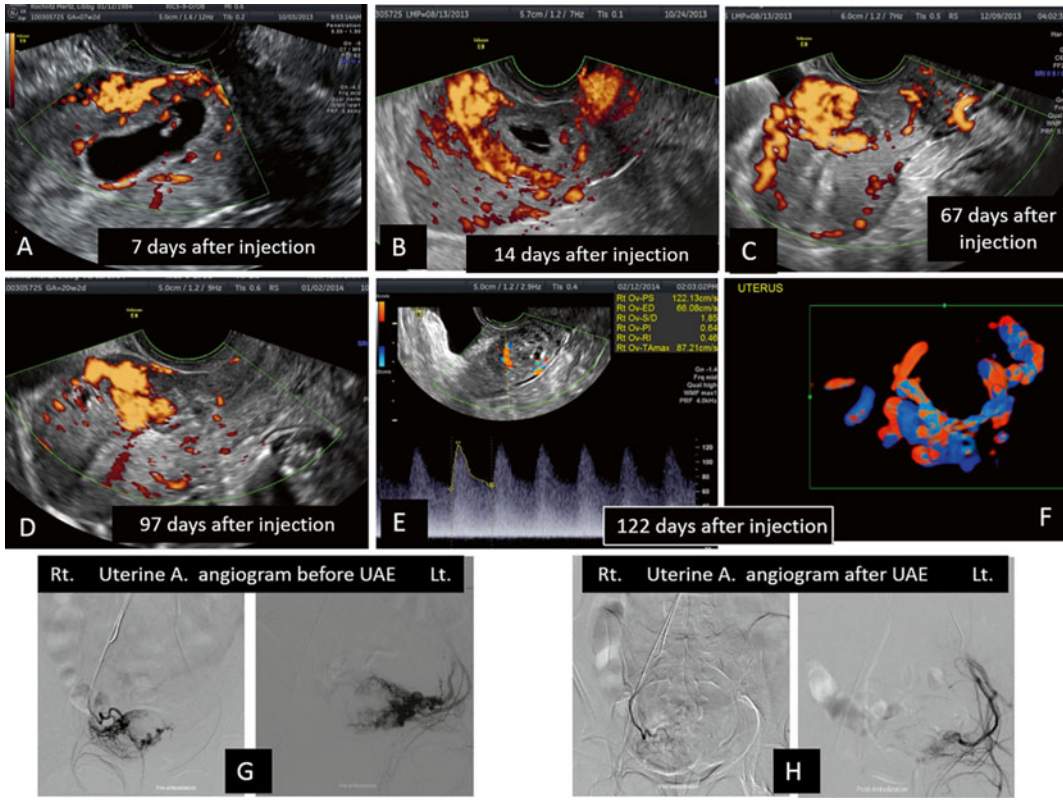

Fig. 17.11 Late development of an AVM after local intragestational injection of MTX injection with sonographic follow-up of the vascularization on days 7, 14, 67, 97, and 122 following the treatment (**a**–**f**). The patient refused an UAE after 4 weeks; however, the continuous vaginal spotting and slight bleeding finally led to the acceptance of the bilateral embolization of the uterine arteries, which was successful (**g**, **h**)

suction aspiration in their patients with CSP for 5 days after UAE. Uterine artery embolization works better combined with other noninvasive and invasive (suction aspiration) treatments [36–38]. In our 60 cases of CSP, UAE was used as a secondary treatment in four patients with persistent vaginal bleeding or developing AVM. Embolization failed to stop the bleeding in one of the patients with AVM, therefore, hysterectomy was performed [24].

If UAE fails, which may be the case, the clinician must contend with a larger gestation applying a secondary treatment. However, it is hard to evaluate its actual complication rates, since some articles have insufficient data to rely on. As stated previously, in our 60 cases of CSP, one of the patients required (and finally agreed to) AVM embolization to stop her continuing vaginal bleeding (as well as her high PSV on Doppler), 122 days after her initial local MTX injection (Fig. 17.11).

Updating this treatment approach with the review of 1223 patients published after 2012, UAE was used alone or in combination in 309 cases with a mean complication rate of 28 %, with its highest rate if combined with intra-arterial injection of MTX, at the time of the catheterization: 18 of 52 (34.6 %).

Excision by Hysteroscopy and/or Laparoscopy

Hysteroscopic and laparoscopic surgery require general anesthesia. The overall complication rate for 108 cases managed by hysteroscopy was

13.8 % [4]. However, no complications were noted if hysteroscopy was combined with transabdominal ultrasound guidance (nine cases were published). The rate of complications increased to 17 % if hysteroscopy was combined with mifepristone. In the hands of an experienced clinician, guided by transabdominal ultrasound, hysteroscopy may be a reasonable way of treatment for CSP [35, 39–45]. The use of an inflatable balloon catheter, after treatment with hysteroscopic excision, may prevent (or treat) possible bleeding from the operative site.

Laparoscopic surgery, alone or in combination, was used to excise the site of the scar pregnancy and repair the anterior uterine wall. Fifty four such cases were published up to 2012 in the reviewed literature, with complication rates between 20 and 30 % [4]. Since 2012, there were several other laparoscopically treated case reports [38, 46–50].

Robotic-assisted laparoscopic removal of CSP was also published [51]. We speculate that the complicated, time consuming and probably costly robotic surgery involving dedicated staff and its availability only in selected medical centers make the use of this operative approach to CSP questionable, since it can be replaced with several office based, simple and less involved treatments.

Methotrexate

One of the most frequently used therapies to treat CSP is undoubtedly methotrexate (MTX). Administered in single or multiple, successive doses, intramuscularly, injected locally into the gestational sac, as intravenous slow drip and finally injected into the umbilical artery at the time of a UAE. It was reported to be administered as a first line or a secondary or backup medication, as a single agent, and/or combined with any other conceivable treatment as an adjunct.

Systemic, "*first-line*," *single-dose MTX* is administered as an intramuscular, single injection. The usual protocols were 1 mg/kg of body weight or 50 mg/m^2 of body surface area. Its complication rate is 62.1 % due to a required second-line treatment, when the fetal heart beat fails to cease after several days [4]. Bodour et al. [52] challenged this result, which prompted a reevaluation of the reviewed material; however, after the more rigorous recounting of the cases, an even higher (66.1 %) complication rate was found [53].

The reason for this, we suspect, may be caused by its slow action and that the results may take days to be seen. We also suspect, that it may not be able to stop cardiac activity and placental invasion. During these several days (or entire week) the gestational sac, the embryo or fetus, and its vascularity continues to grow, forcing a secondary treatment that must be able to handle a larger gestation with more abundant vascularization. The slow action of systemic MTX treatment is echoed, among others, in the series of Yin et al. [54]. It is true that there are also proponents of the use of systemic MTX as a single agent; however, it is impossible to attribute the cessation of the heart activity to the effect of MTX, since at least 10 % of first-trimester intrauterine pregnancies undergo a spontaneous demise.

Based upon our recent review of 1223 cases of CSP, there were 236 cases in which MTX was administered as a single agent or in a combined fashion with other treatments, with a mean of 21.4 % complications. Methotrexate used alone (as single or multi-dose) lead to 38 % of the cases needing a secondary treatment [35, 55]. Combined with D&C (26 cases), another therapy with high complication rate, all needed a secondary treatment.

Systemic, *sequential*, *multidose use of MTX*. The injected amounts of MTX are similar to the dose for the single-dose regimen. However, two to three intramuscular injections (1 mg/kg of body weight or 50 mg/m^2 of surface area) are given at an interval of 2 or 3 days over the course of a week. In this case one should be aware of the cumulative, adverse effects of this drug on the liver and bone marrow, since the total amount is higher than in the single dose regimen. In fact, even multidose treatments have failed [56]. Some combine it with different doses of leucovorin, which protects against unwanted and adverse

systemic effects (termed "rescue" regimen). Several articles expressed their authors' confidence in support of systemic multidose MTX treatment [57].

It is difficult to assess the complication rate associated with the above approach because it was often used in conjunction with, or after "first-line" or even after "secondary" treatments [54]. It is clear that MTX can successfully be applied as an adjunct and combined with other mostly nonsurgical treatments. The drawback of both treatments is the long waiting time to observe their effect. If they fail to stop the heart and quickly lower the levels of hCG, a secondary treatment has to deal with a larger gestation and vascular supply.

Intra-arterial or intravenous MTX treatment. Adopted and used in China—a total of 193 patients were treated using intravenous or intra-arterial administration of MTX solution. The intra-arterial route is used at the time of UAE. Most intravascular treatments were combined with other methods such as suction aspiration laparoscopy, hysteroscopy and D&C. Li C et al. [58] treated 33 patients with CSP out of 13 patients treated with intravenous MTX. Three of the 13 required hysterectomy for profuse bleeding. Zhang Y et al. [59] has a series of 96 patients of which 33 had intravenous MTX treatment. Since most patients, however, were treated in combination with other methods, their outcome is unclear from the English abstract. Another method is to infuse MTX solution into the uterine artery at the time of UAE. An et al. [60] treated 22 patients with UAE and intra-arterial MTX infusion: 6 patients had severe hemorrhage, 12 had abdominal pain and 4 hysterectomies were necessary. As opposed to this Lan et al. [61] successfully used 50 mg MTX infused into the uterine artery at the time of UAE in 79 patients.

Excision by Hysteroscopic Guidance Alone or in Combination

In our first review [4], hysteroscopic excision was used alone or with other treatments in 113 cases, with a mean complication rate of 18.4 %, which is reasonably low in comparison to other treatment methods. General anesthesia is required for the procedure.

In the literature published after 2012, we found 63 cases managed by this method alone or combined, usually, with laparoscopy [46, 59, 62–65].

Excision by Laparoscopic Guidance

Mostly used as the sole, standalone treatment, since it provides a final solution removing the gestational sac and the tiny placenta. General anesthesia is required. Fifteen of the 49 cases (30.6 %) described in the literature published before 2013 involved complications, as opposed to the 94 cases published in or after 2012 [35, 38, 46, 47, 49, 50, 64, 65], which experienced only 7.7 % in complications when hysteroscopy and laparoscopy were combined. The small numbers may not allow meaningful evaluation of the latter two approaches.

Excision by Laparotomy

Only a handful of articles were published, about 15 patients undergoing excision of the gestational sac using this, relatively involved, surgery procedure, which is usually performed under general anesthesia [46, 65–67]. At times, elective laparotomy was the treatment of choice to perform hysterectomy or it was used as a solution to treat bleeding complications [60, 68–71]. Figure 17.12a depicts the closed suture line after the excision of a CSP while Fig. 17.12b shows the local results after 1 year.

Transvaginal Surgical Excision

Requires a skilled surgeon and used electively in 119 patients with a relatively low (mean 9.7 %) complication rate [72–75]. Li et al. [35] described this surgical approach, which elevates the bladder, excising the gestational sac after curetting and, finally, suturing the area. They managed

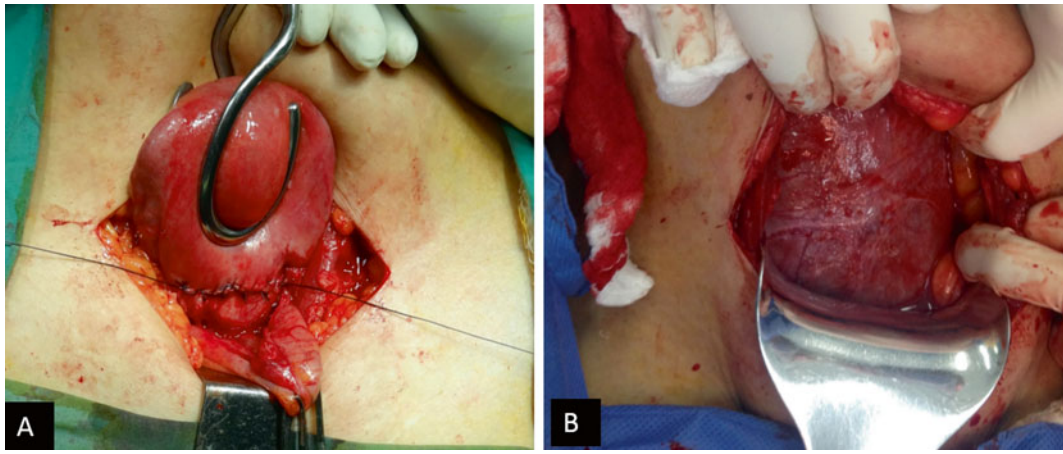

Fig. 17.12 Excision of a CSP sac and the resulting repair (**a**) as well as a follow-up picture 1 year after a previously performed excision and repair (**b**). Courtesy of Dr. Jose Palacios Jaraquemada, Argentina

49 cases, reporting that, despite 18 % minor complications, the procedure is easy and safe. Three patients had intrauterine pregnancies at 6 and 12 months postoperatively. One patient had a recurrent CSP and repeat transvaginal surgical excision. Another patient had an intrauterine pregnancy 5 months postoperatively, however, D&C was performed to prevent uterine rupture.

Intragestational-Sac Injection of Methotrexate or Potassium Chloride, with Continuous, Real-Time Ultrasound Guidance

No anesthesia required. This approach (Fig. 17.13) had the fewest and least-involved complications. In certain cases we completed the local injection by an immediate placement of a Foley balloon catheter that, after inflation with several ml of saline solution, can be kept in place for several days to prevent vaginal bleeding (Fig. 17.14a–f). Of the 83 cases, only 9 (10.8 %) involved complications. Cases performed with transabdominal sonography guidance had a slightly higher complication rate (15 %) than those using TVS guidance. Since 2012 several authors used this simple treatment in 53 patients.

Since the publication of our review, a handful of articles reported on the successful use of the local, intragestational sac injection of ethanol [64], MTX [56, 76–79] and KCl [55] in a total of 53 patients with a complication rate of 5.8 %. Yin et al. [54] treated 20 of 34 patients with CSP by local, transvaginal ultrasound-guided intragestational sac injection of MTX, without complications. Yamaguchi et al. [79] treated eight CSP cases, using intragestational injection of MTX, guided by TVS. Two of the patients needed additional local or systemic MTX injection. The time to the hCG normalization was a mean of 78.5 days (range, 42–166 days). Four of the five patients went on and had pregnancies after the treatment and had uneventful parturition, however, another CSP was diagnosed in one patient. Pang et al. [77] successfully treated three patients with local, intragestational MTX injection. Some providers prefer the use of KCl for all their local injections in all types of ectopic pregnancies including CSP [80]. KCl is exclusively used to inject heterotopic pregnancies to enable the normal development of the intrauterine gestation.

Local, intragestational sac injections render *final solution* by stopping the heart activity and it appears to be the most effective and simple intervention for first-trimester CSP between 6 and 8–9 weeks and can be performed by TAS or TVS guidance. This treatment may be even more relevant for patients desiring future fertility.

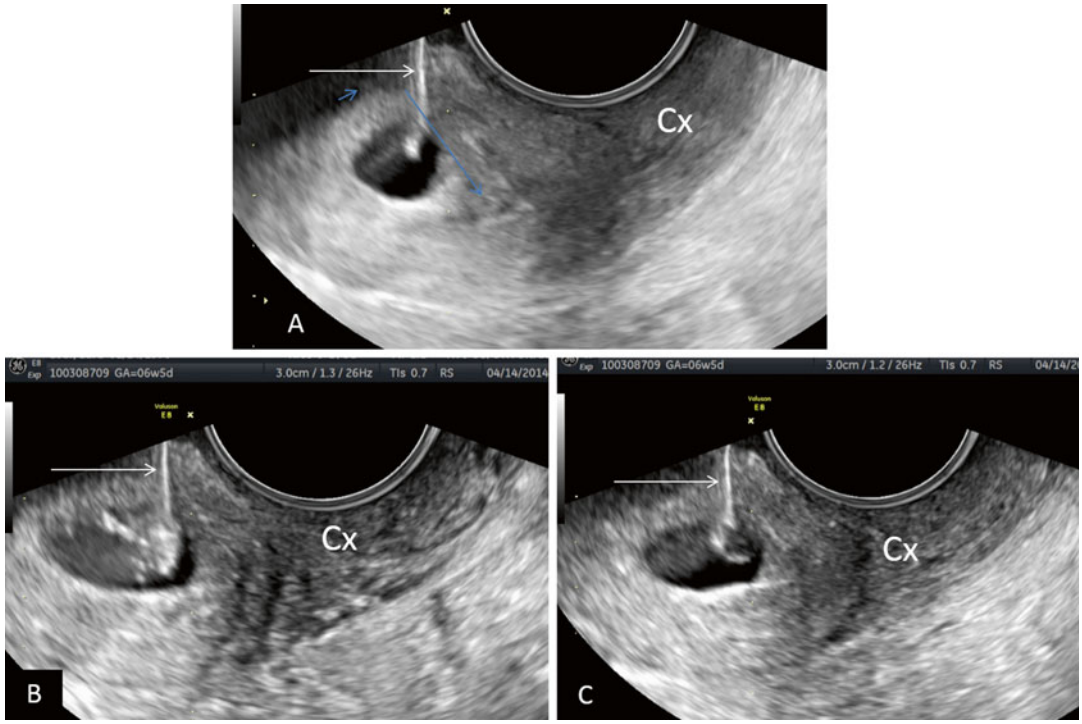

Fig. 17.13 Transvaginal ultrasound guided transvaginal, local injection of a CSP. The needle approach into the chorionic sac (**a**), insertion into the embryo (**b**) and targeting the yolk sac (**c**) trying to damage it with a rotation of the needle

Shirodkar Suture in the Treatment of CSP

Used by Jurkovic et al. [81], during the evacuation of a cesarean scar pregnancy, it is an effective method for securing hemostasis. In their view, it minimized the need for blood transfusion and ensured preservation of fertility.

Foley Balloon Catheters as an Adjuvant to Other Treatments to Prevent/Control Bleeding

A creative and, relatively new, approach to the treatment is inserting a Foley balloon catheter that is inflated at the site of the CSP, alike the Bakri balloon in cases of obstetrical hemorrhage [32, 82–84]. We used this approach as an adjuvant to treatments of CSP [31]. Even so, this approach is almost always used in a planned fashion, in conjunction with another treatment or as backup, if bleeding occurs (Fig. 17.15a–h). Catheters may be kept in place for as long as 3–4 days, according to the individual case, provided antibiotic coverage is prescribed. As stated above, this approach is almost always used in a preplanned case of a patient who restarted bleeding 23 days after local injection of MTX, with a relatively large gestation of 9 weeks 3 days. Inflating the balloon to 20 ml controlled bleeding (Fig. 17.16).

Recurrent CSP

Patients treated in the first trimester for CSP, should be informed that such a gestation may not happen again in a future pregnancy since the risk is about 1 % for reoccurrence. In the literature

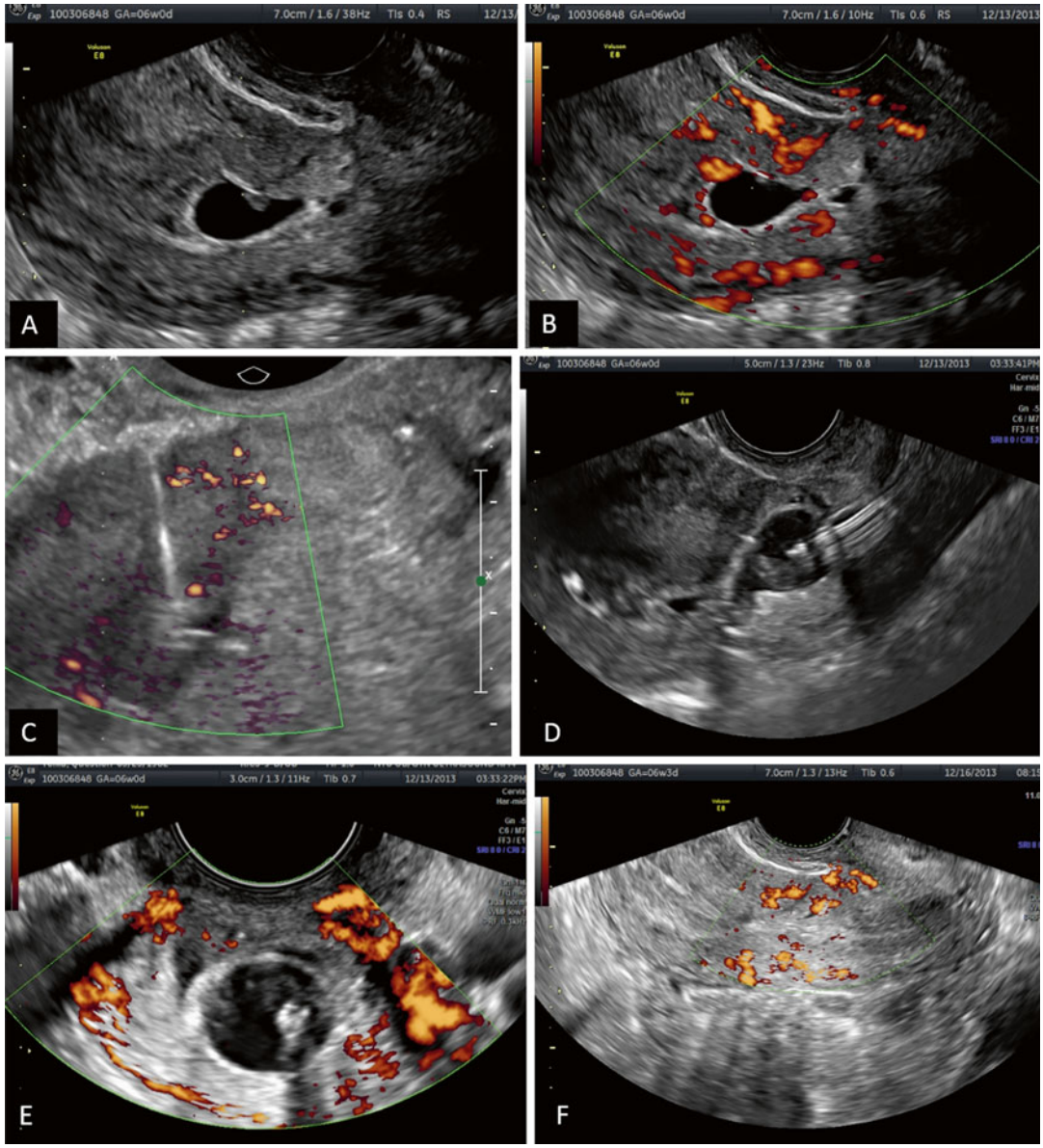

Fig. 17.14 Sequential images of treating a 5–6 week live CSP using local injection followed by insertion of a Foley balloon. (**a**) Sagittal image showing the gestational sac in an anterverted/anteflexed uterus. (**b**) The vascularization is evident. (**c**) The needle was inserted under transvaginal ultrasound guidance and MTX was injected. (**d**) The inflated balloon in situ creating pressure on the surrounding tissues. (**e**) Transverse image of the inflated balloon with barely detectable blood vessels. (**f**) The area 3 days later after removal of the balloon. Minimal vascularity was seen and the minimal vaginal bleeding stopped after 1 week

Fig. 17.15 (continued) MTX would suffice as treatment. (**b**) At 5 weeks 4 days embryonic heart beats were seen. (**c**) A transverse section demonstrates the anterior placenta with its vessels between the sac and the bladder. (**d**) 3D Doppler angiography clearly shows the rich vascular web below the bladder. (**e**, **f**) After local, intragestational injection of MTX a Foley balloon was inserted. The compressed sac is seen. (**g**, **h**) Two hours after balloon insertion diminished blood flow was observed around the sac by Doppler interrogation

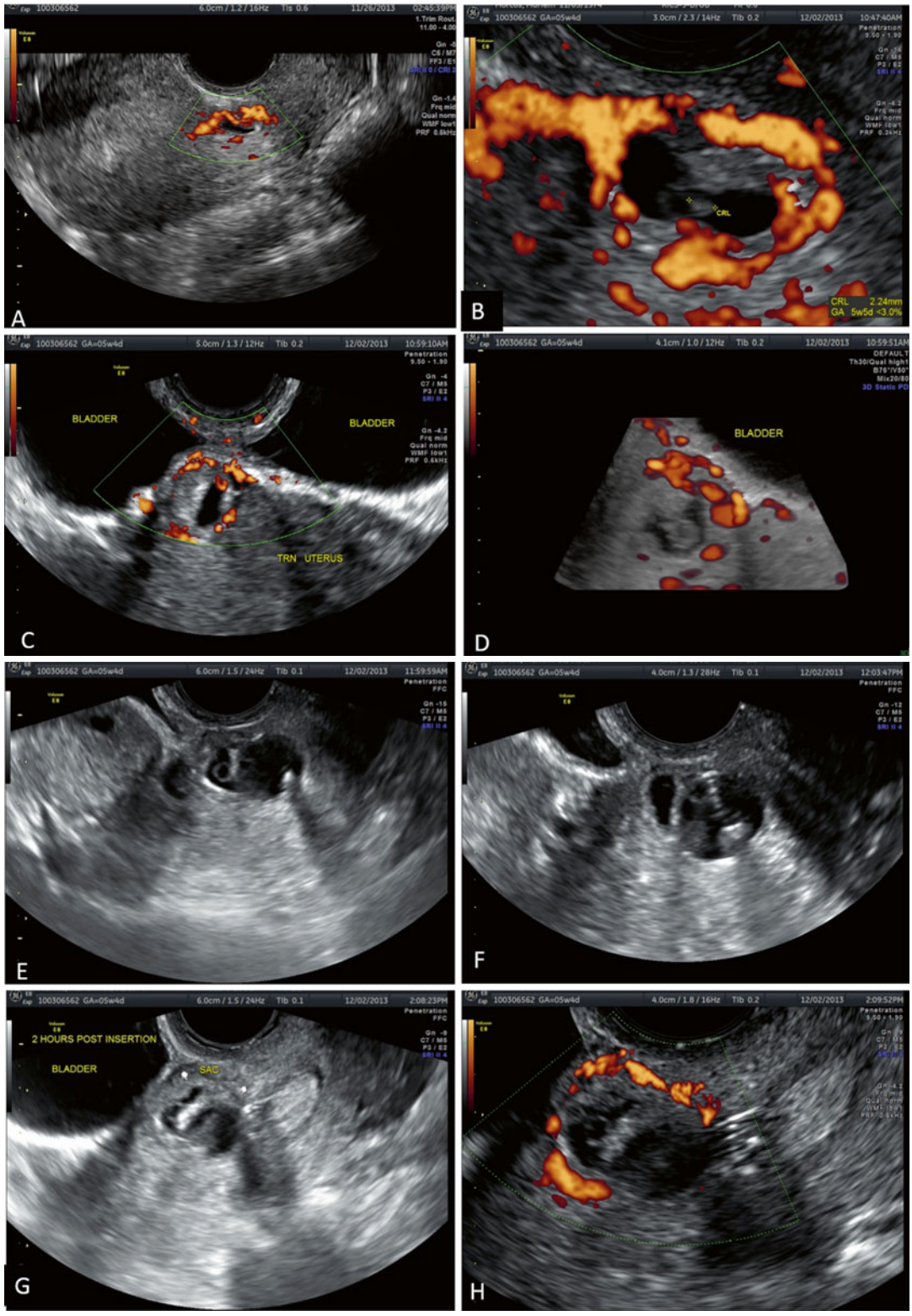

Fig. 17.15 Sequential, pictorial demonstration of the treatment of a 4 week 5 day CSP and use of a Foley balloon catheter. (**a**) The sagittal, power Doppler image at 4 weeks 5 days. The patient selected to wait if systemic

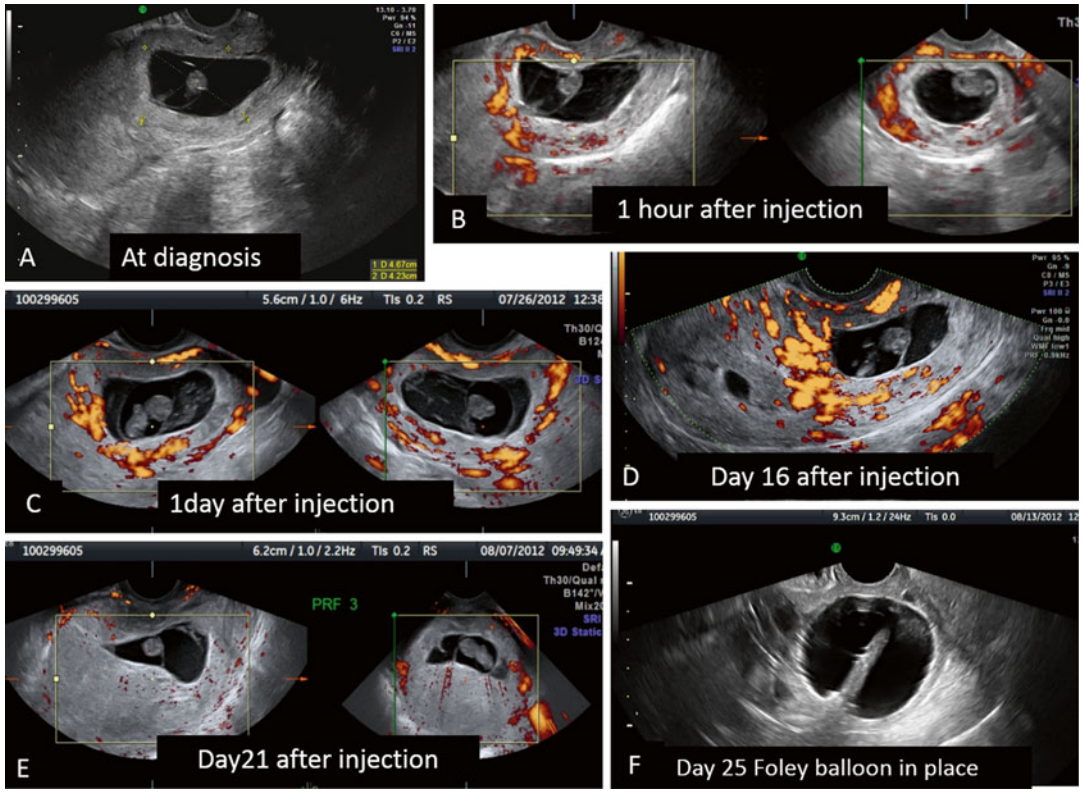

Fig. 17.16 The use of Foley balloon catheter in a patient with a relatively advanced CSP of 9+ weeks with a gestational sac of 4.4×4.3 cm treated by local intragestational injection of MTX and who started to bleed late, 25 days after treatment. (**a**–**e**) Sequential power Doppler ultrasound images from diagnosis and immediately after the local injection of MTX stopping the heart beats and throughout days 1, 16 and 21 after treatment. No vaginal bleeding was reported, however, no real decrease of the sac size occurred and the small embryo was still visible in the sac. (**f**) On day 25 after the initial treatment vaginal bleeding occurred, which was successfully treated by insertion of a Foley balloon catheter and inflated to about 4 cm diameter by about 20

reviewed through 2012, seven recurrent cases of CSP were described [4]. Gupta et al. [12] provided an additional case, with a patient who had four consecutive CSPs within 2 years. Please note, this patient became pregnant with the fifth CSP, decided to continue the pregnancy, and at the time of this writing, is 16 weeks pregnant.

Multifetal CSP

Rare but possible, two gestational sacs with two embryos can be present as a twin CSP (Fig. 17.17). There was also a triplet CSP published. Their treatment, so far, was to terminate the pregnancies.

Heterotopic CSP

Several heterotopic pregnancies were reported. In these cases the intrauterine pregnancy can result in live offspring (Fig. 17.18). Several articles reported heterotopic IUP and CSP. The best review, however, containing detailed information is by Ugurlucan et al. [85]. Heterotopic CSP after CS may occur especially when a pregnancy follows assisted reproductive technology. These pregnancies are usually managed by selective injection of the scar pregnancy by local intragestational injection of KCl and laparoscopic excision [86, 87]. Fortunately, most intrauterine pregnancies can be preserved after treatment.

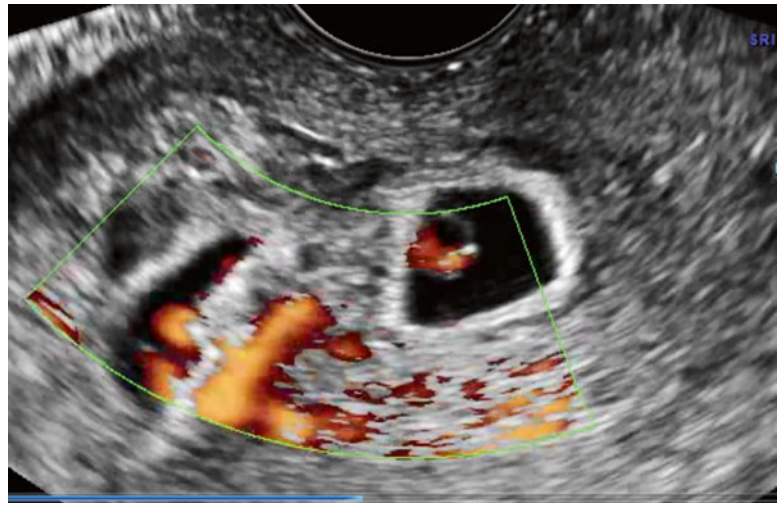

Fig. 17.17 Twin CSP in the scar with active heart activity in this 5 week 5 day pregnancy. Local, intragestational MTX was performed using one single needle insertion slightly adjusting the needle direction to reach both sacs

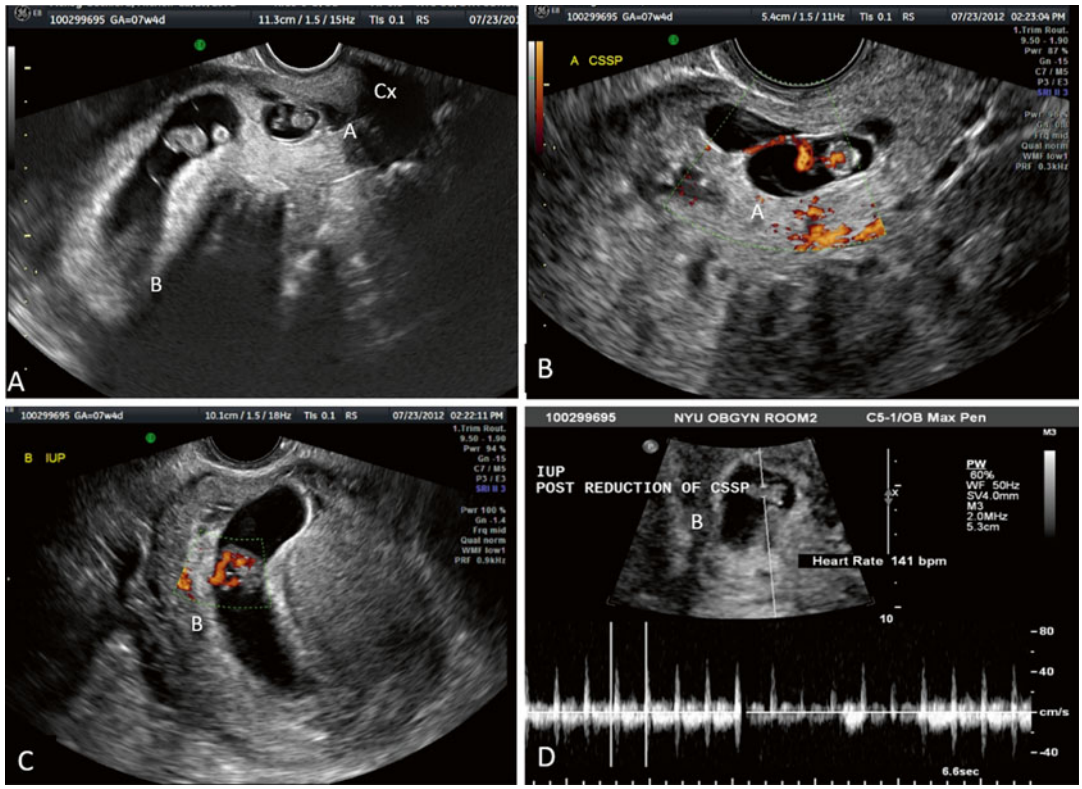

Fig. 17.18 Heterotopic CSP and IUP at 7 weeks and 4 days. (**a**) Panoramic, sagittal view of the two sacs. Both embryos were alive. The intrauterine sac (*B*) is filling the available space in the uterine cavity (*Cx* cervix). (**b**) Image of the embryo (*A*) in the lower anterior sac. (**c**) Image of the intrauterine embryo (*B*) in the upper sac. (**d**) Proof of the heart beats of the intrauterine embryo moments after the injection of the scar pregnancy. The patient delivered at term a healthy neonate

Summary

Cesarean scar pregnancy is *not* an ectopic pregnancy by definition. Contrary to *real* ectopic pregnancies, the CSP is in the uterine cavity and if not terminated (based upon the recently available literature) can result in a live offspring. CSP is a relatively rare but dangerous and complicated-ridden clinical entity, closely related to a consequence of CDs.

The best diagnostic tool for its detection, and at times for treatment, is transvaginal sonography. In addition transabdominal and color Doppler ultrasound provide satisfactory diagnostic information. The main differential diagnostic entities of a CSP are cervical pregnancy and a miscarriage in progress. Patients with CSP should be counseled based upon new, peer-reviewed evidence published in the latest literature. In addition, patients must be informed of the possible second- and third-trimester complications.

There is mounting evidence that every patient with previous CD should be screened for CSP, as soon as possible. Also, there has been evidence of first-trimester MAP. CSP and MAP share the same histologic picture, as CSP is a precursor of MAP. Most patients with a CSP diagnosed in the first trimester will by the third trimester have MAP. And almost all repeat CD will have hysterectomy.

There is no single best treatment approach to terminate CSP with positive heart activity. Therefore, the procedure with the least complications should be considered and performed without delay. Single-dose systemic MTX injection is a lengthy and usually ineffective first line therapy, delaying the final treatment. MTX, however, as an adjuvant to other treatments has a proven efficacy. Ultrasound guided local, intragestational sac injection of MTX/KCl is simple and has low complication rates. Sharp curetting of the CSP site can cause severe bleeding. Uterine artery embolization alone is less effective as a single, first line treatment but has proven useful as an adjunct to other therapies and in cases of emergency due to sustained vaginal bleeding. Insertion and inflation of a Foley balloon catheter is effective to prevent or treat bleeding from the site of a CSP, following local injection or endoscopic treatment of CSP. Attention should be given to the possibility of recurrent multifetal and heterotopic CSP.

Teaching Points

- Diagnose a cesarean scar pregnancy by the diagnostic criteria and differentiate it from cervical pregnancy and/or a spontaneous abortion.
- Realize that there is a common histologic basis of cesarean scar pregnancy and morbidly adherent placenta (accreta, increta and percreta).
- Construct a counseling and a management plan for the CSP taking into consideration patients' obstetrical goals and evidence based management.

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First-Trimester Ultrasound in Gestational Trophoblastic Disease

18

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Introduction

Gestational trophoblastic disease (GTD) is a series of conditions that arise from the trophoblastic epithelium of the placenta. The specific histologic subtypes of GTD are hydatidiform mole (complete or partial), invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). All types of GTD share a common tumor marker, human chorionic gonadotropin (hCG). Approximately 90 % of cases of GTD are complete (CHM) or partial (PHM) hydatidiform moles, which are noninvasive, localized neoplasms resulting from an abnormal fertilization event [1–4]. CHM arise from fertilization of an empty egg, are usually diploid with a 46XX karyotype and androgenetic, while PHM are the result of fertilization of a normal ovum with two spermatozoa and thus have a triploid karyotype [5]. The remaining 10 % of GTD include patients who develop malignancy following either a molar or nonmolar pregnancy [4].

The incidence of CHM ranges from 23 to 1299 cases per 100,000 pregnancies with wide variations reported between different regions of the world [6]. The main risk factors are maternal age over 35 and history of prior GTD. GTD often presents with abnormal bleeding and an elevated hCG. Preceding wide accessibility of ultrasound in early pregnancy, classic findings of CHM on presentation included an enlarged uterus (size > dates), absent fetal heart tones, markedly elevated hCG for gestational age, pelvic pressure or pain, theca lutein cysts, vaginal bleeding and subsequent anemia, hyperemesis gravidarum, hyperthyroidism, and preeclampsia before 20 weeks [7]. PHM usually present as a missed abortion. Treatment for CHM and PHM includes uterine evacuation and post-evacuation monitoring of quantitative hCG levels to detect post-molar gestational trophoblastic neoplasia (GTN). Monitoring of the hCG level is critical as the risk of GTN is approximately 15–20 % after CHM

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and 1–5 % after PHM pregnancy [2]. Treatment for GTN includes chemotherapy and occasionally surgical intervention.

Ultrasound plays an important role in managing patients with GTD, not only for the initial diagnosis of molar pregnancy and GTN, but also in the evaluation of patients who present with recurrent and resistant disease as well as for the long-term follow-up. Recent studies also demonstrate that it may be prognostic in identifying patients with GTN at risk for chemoresistance.

Ultrasound in the Diagnosis of Molar Pregnancy

Classic Sonographic Findings of Molar Pregnancy

Classic sonographic findings of a CHM include an enlarged uterus with complex heterogeneous material in the absence of a normal-appearing intrauterine gestation. Descriptions of CHM pregnancy include "snowstorm" appearance or a "cluster of grapes," which represent the enlarged hydropic villi [8, 9] (Fig. 18.1). A partial molar pregnancy, on the other hand, may show an enlarged placenta with multiple anechoic spaces along with fetal parts representing a nonviable embryo or fetal anomalies and growth restriction as a result of triploidy [8, 10–12] (Fig. 18.2). Historically, only 30–47 % of patients were diagnosed with a complete molar pregnancy in the first trimester. However, the increased use of ultrasound in early pregnancy has led to over 84 % of diagnoses of CHM being made in the first trimester [7].

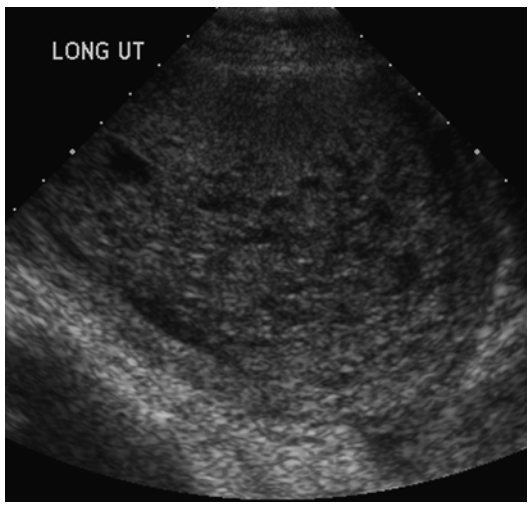

Fig. 18.1 Complete hydatidiform mole with classic diffuse vesicular changes. Figure provided by Dr. Carol B. Benson, Director of Ultrasound, Department of Radiology, Brigham and Women's Hospital and Professor of Radiology, Harvard Medical School, Boston, MA

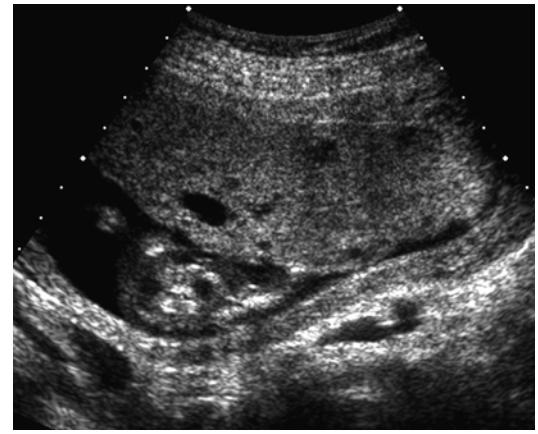

Fig. 18.2 Partial hydatidiform mole with focal vesicular changes and nonviable fetus. Figure provided by Dr. Carol B. Benson, Director of Ultrasound, Department of Radiology, Brigham and Women's Hospital and Professor of Radiology, Harvard Medical School, Boston, MA

Ultrasound Diagnosis of Early Molar Pregnancy

The classic sonographic appearance of CHM described above may be lacking in patients who present with bleeding early in the first trimester, making the sonographic diagnosis more difficult. The hydropic villi are smaller at earlier gestational ages and the molar tissue may appear as a complex echogenic intrauterine mass with several anechoic or cystic spaces [10, 13] (Fig. 18.3). In early gestations it may also be more difficult to differentiate PHM from CHM. One characteristic that may help to differentiate the two types of molar pregnancy is the presence of a gestational sac in PHM that is either empty or contains small fetal echoes surrounded by a large rim of placental echoes with cystic spaces [14]. Additionally, the earlier the presentation the more difficult it is

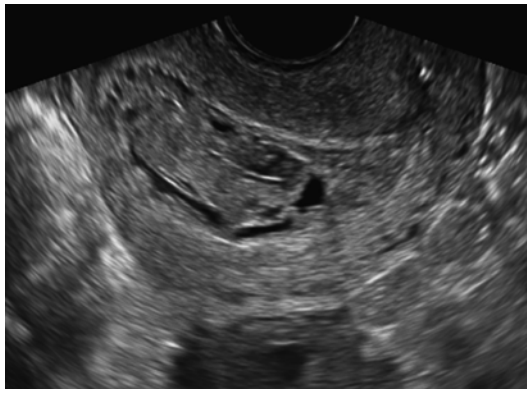

Fig. 18.3 First-trimester complete hydatidiform molar pregnancy with limited vesicular changes that are less prominent and best seen on transvaginal ultrasound images. Figure provided by Dr. Carol B. Benson, Director of Ultrasound, Department of Radiology, Brigham and Women's Hospital and Professor of Radiology, Harvard Medical School, Boston, MA

to differentiate molar pregnancy from a hydropic nonmolar abortion. Ultrasonic descriptions of early histologically confirmed molar pregnancies include: an empty gestational sac or intrauterine anechoic fluid collection, fluid collection in association with an echogenic mass, thickened endometrium and echogenic fluid-filled levels within the endometrium [15, 16].

Ultrasound can also be used to assess the volume of molar tissue present in the uterus which has been shown to be a risk factor for GTN [17–20]. A three-dimensional assessment of volume is felt by some experts to be superior to a single measurement. However, in one study the size of the lesion measured sonographically was not predictive of need for chemotherapy [18]. Although myometrial invasion can be assessed with ultrasound, MRI is often a better modality to demonstrate the presence of invasion of molar tissues into the uterine wall [19, 20].

Sensitivity of Ultrasound in Detecting Molar Pregnancy

Several investigators have examined the accuracy of ultrasound in diagnosis of molar pregnancy. Fowler et al. [21] published the largest study evaluating the role of ultrasound in detection of molar pregnancy. The authors reviewed 1053 consecutive cases of molar pregnancy with early ultrasound evaluation and found that the sensitivity for detecting either a CHM or PHM was 44 %. The mean gestational age at diagnosis was 10 weeks. They found that ultrasound was better at detecting CHM versus PHM (79 % vs. 29 %, $p<0.0001$) and there was a false-positive rate of 10 % whose final pathology demonstrated hydropic degeneration of nonmolar pregnancies. Other smaller reviews have shown sensitivity of ultrasound in detecting molar pregnancy to range from 34 to 57 % [15, 16, 21, 22]. Correlation with hCG is critical to the diagnosis. It has been shown that the ultrasonographic diagnosis of complete molar pregnancy is facilitated by clinical factors such as hCG [23]. When analyzing ultrasound sensitivity by type of molar pregnancy, ultrasound is consistently more sensitive in detecting CHM (sensitivity range 58–95 %) [13, 16, 21–24] as compared to PHM (sensitivity range 17–29 %) [16, 21, 22]. The sensitivity of ultrasound improves with increasing gestational age as the hydropic villi grow in size with advancing gestational age and are more easily seen by ultrasound.

Mimics of Molar Pregnancy

There are other conditions in early pregnancy that mimic the sonographic appearance of molar pregnancy such as hydropic degeneration of the placenta, missed abortion, blighted ovum and retained products of conception. False-positive rates of ultrasound in molar pregnancy have been estimated anywhere from 4 to 10 % [21, 25]. Hydropic changes of the placenta in other gestations can appear similar to the hydropic villi of molar disease but tend to be less homogeneously distributed [21, 26]. Although it can be difficult to differentiate an early partial molar pregnancy from other abnormalities of early pregnancy, the presence of an echogenic rim around the sac may be more indicative of a missed abortion or blighted ovum [14].

Color Doppler Ultrasound in Diagnosis of Molar Pregnancy

Color Doppler ultrasound allows the clinician to assess vascularity. In trophoblastic tissues a high velocity, low resistance flow is consistent with increased vascularity. Thus, use of color Doppler imaging may help differentiate molar pregnancy from mimics such as missed abortion [10, 27].

Uterine Artery Doppler Measurement in Molar Pregnancy and Development of GTN

Several studies have shown that uterine artery resistive indices correlate well with hCG levels and may therefore be helpful in diagnosis and monitoring of treatment [28–33]. Yalcin et al. followed 21 patients with molar pregnancy with hCG and uterine artery Dopplers and found significant negative correlations with hCG and Doppler indices, i.e., as the hCG declined demonstrating resolution of disease, the resistive indices rose [31]. In this study, the patients who ultimately developed postmolar GTN had significantly lower Doppler indices than those whose disease regressed spontaneously. Others have also demonstrated this inverse relationship of lower resistive indices indicating a greater risk of developing postmolar GTN [29, 30, 34–36]. Finally, one study of 25 patients with molar pregnancy undergoing surveillance with hCG and transvaginal ultrasound (TVUS) with Doppler also noted that surveillance with Doppler predicted GTN 1–3 weeks before routine hCG monitoring and that ultrasound findings tended to resolve about 8 weeks earlier than hCG normalization [32].

Ultrasound in the Diagnosis and Management of Ovarian Theca Lutein Cysts

Ovarian theca lutein cysts develop in 25–65 % of complete molar pregnancies in association with markedly elevated hCG levels >100,000 mIU/ml. In a review of 386 patients with untreated hydatidiform mole, 102 patients (26.4 %) had concurrent theca lutein cysts [37]. Theca lutein cysts appear sonographically to be anechoic, multiloculated ovarian cysts [38] (Fig. 18.4). Mean cyst diameters are reported around 7 cm but can range in size from 3 to 20 cm [26, 38]. Typically these cysts will be accompanied with the uterine sonographic findings detailed previously. Of note, theca lutein cysts are less likely to be seen in the first trimester complete or partial moles pregnancies where the hCG level is generally <100,000 mIU/ml [15]. The size of the theca lutein cysts has not been shown to correlate with persistent disease, although the presence of bilateral cysts is associated with an increased risk of GTN [37]. Serial ultrasound examination is useful to monitor the regression of theca lutein cysts which tend to regress slowly over 2–4 months following molar evacuation as the hCG level declines [39]. Although theca lutein cysts rarely rupture spontaneously or undergo torsion, prompt laparoscopic intervention can be used effectively. The use of ultrasound guidance during percutaneous drainage of massively enlarged theca lutein cysts may also provide considerable relief of abdominal discomfort.

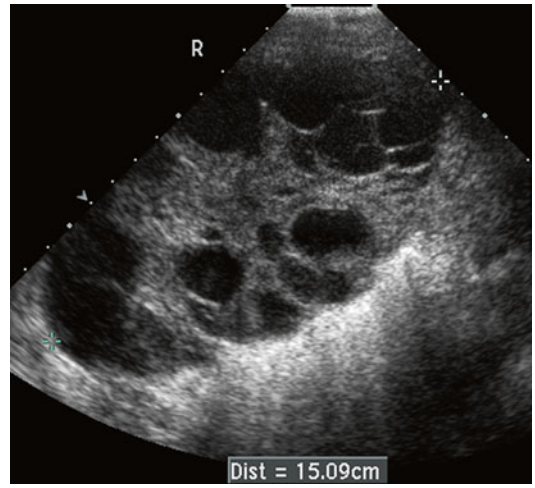

Fig. 18.4 Theca lutein cysts filling an ovary and appear as anechoic multi-loculated cystic structures. Figure provided by Dr. Carol B. Benson, Director of Ultrasound, Department of Radiology, Brigham and Women's Hospital and Professor of Radiology, Harvard Medical School, Boston, MA

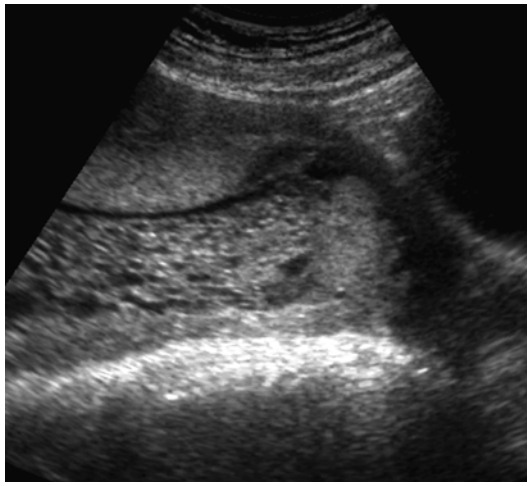

Fig. 18.5 Twin gestation with one normal placenta anteriorly and one complete molar pregnancy posteriorly demonstrating classic diffuse vesicular changes. Figure provided by Dr. Carol B. Benson, Director of Ultrasound, Department of Radiology, Brigham and Women's Hospital and Professor of Radiology, Harvard Medical School, Boston, MA

Ultrasound in the Diagnosis of Molar Pregnancies with a Coexistent Twin

Concurrent twin pregnancy with a hydatidiform mole and coexisting fetus is estimated to occur 1 in 22,000–100,000 pregnancies [40]. The diagnosis of a molar pregnancy with coexisting fetus is almost always made based on ultrasound findings and tends to be diagnosed at later gestational age than a singleton CHM [41]. Ultrasound findings show a live fetus with either a single enlarged placenta with the classic cystic changes and increased echoes or there may be two placentas, one normal and one molar [42] (Fig. 18.5). Ultrasound is also critical in the ongoing management of these pregnancies to help ensure the well-being of the coexisting fetus. Of those pregnancies described in the literature that were continued after diagnosis of a twin molar gestation, more than half continued beyond the 28th week of gestation with almost 70 % of children surviving [40]. The rate of GTN was not significantly different between the group who chose to continue the pregnancy and those that interrupted the pregnancy at diagnosis. However, these twin molar pregnancies are more likely to develop GTN as compared to singleton molar pregnancies [41].

Ultrasound in the Evacuation of Molar Pregnancy

The first step in management of a molar pregnancy is uterine evacuation, typically with suction curettage [43]. The technique for uterine evacuation is similar to that used for spontaneous and induced abortions. However, there is a greater concern for blood loss due to the increased vascularity of molar gestations. Intraoperative ultrasound may be a very useful tool during a suction curettage for molar pregnancy, particularly in cases with a large volume of intrauterine disease. When available, ultrasound should be used at the start of the procedure to examine the intrauterine disease and assess for pelvic extension. Ultrasound can be utilized to help prevent uterine perforation during the serial dilation of the cervix and placement of the suction curette. Finally, at the conclusion of the procedure, ultrasound allows the clinician to visualize the uterine cavity and confirm complete evacuation of molar tissues [43].

Ultrasound in the Diagnosis and Management of GTN

Gestational trophoblastic neoplasia (GTN) includes invasive mole, choriocarcinoma, PSTT, and ETT. Choriocarcinoma arises from both cyto- and syncytio-trophoblast and produces high levels of hCG. Choriocarcinoma is associated with early metastatic spread but is generally highly sensitive to chemotherapy. Unlike choriocarcinoma, PSTT and ETT arise from extravillous intermediate trophoblasts and produce low levels of hCG. Unfortunately and importantly, both PSTT and ETT are relatively resistant to chemotherapy unlike the other types of GTN. Ultrasound is the imaging modality of choice for the initial evaluation of the uterus and adnexa when a patient has been diagnosed with GTN. Ultrasound is not able to differentiate between types of GTN. Therefore, correlation with clinical history and hCG is critical. Betel et al. compared 17 cases of GTD to 14 cases of retained products of conception sonographically and found that GTD cases were more likely associated with a larger mass (>3.45 cm), thin endometrium (<12 mm),

myometrial based mass and vascular lakes [44]. Non-gestational conditions that have been described to mimic GTD sonographically include uterine leiomyomas and an adenomyomatous polyp [26, 45]. In addition to the increased vascularity, Doppler can also illustrate focal areas of increased flow within the myometrium in cases of invasive molar pregnancy and choriocarcinoma [46]. Measurement of uterine artery Doppler indices including the resistive index (RI) and the pulsatility index (PI) has been studied in GTN. RI and PI tend to be very low in GTN and changes within these indices correlate with response to treatment and resolution of GTN over the course of follow-up with the indices increasing as the hCG levels decline [47, 48]. Nonetheless, some sonographic findings may be clues to the diagnosis.

- *Invasive molar pregnancy* may appear as intrauterine mass(es) with anechoic areas and also often demonstrates focal areas of increased echogenicity within the myometrium or can appear as heterogeneous lesions containing fluid-filled cavities representing invasion (Fig. 18.6).
- *Choriocarcinoma* may appear as an enlarged uterus containing a semisolid heterogeneous echogenic mass with areas of necrosis and hemorrhage. Choriocarcinoma nodules are hypervascular showing increased vascularity on color Doppler. Choriocarcinoma can also be seen invading the myometrium or even out to the parametria.
- *Placental site trophoblastic tumor* may also appear as small heterogeneous echogenic areas with fluid filled cysts, but generally has less necrosis than choriocarcinoma. PSTT may also appear as a solid tumor with or without cystic spaces in the uterus or invading the myometrium. These masses can demonstrate a wide range of vascularity from a non-vascularized mass to a high degree of vascularity [48, 49].
- *Epithelioid trophoblastic tumor* appear early in the course of disease with irregular echolucent lacunae within the myometrium on transvaginal ultrasound, but later in the disease with a well-circumscribed solitary echogenic lesion in the fundal myometrium without blood flow [50].

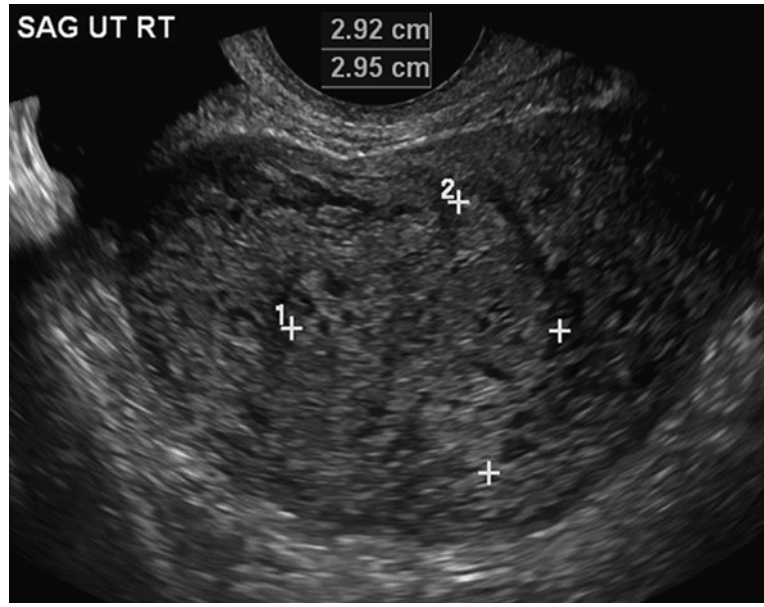

Fig. 18.6 Invasive complete molar pregnancy with intrauterine mass containing diffuse vesicular changes invading into the myometrium. Figure provided by Dr. Carol B. Benson, Director of Ultrasound, Department of Radiology, Brigham and Women's Hospital and Professor of Radiology, Harvard Medical School, Boston, MA

Ultrasound to Assess Presence and Volume of Intrauterine Disease

Transvaginal ultrasound (TVUS) is the preferred technique to detect the presence of invasive GTN [29, 51, 52]. TVUS findings of GTN are described as hypoechoic areas in the endometrium and intramyometrial nodules [53], clusters of high amplitude echoes within the myometrium representing invasive tumor with echo-free areas representing hemorrhage [54], and multiple "serpinginous anechoic channels" throughout the central part of the uterus [51].

Ultrasound Evaluation for Postmolar GTN

Following diagnosis and evacuation of a CHM or PHM, serial hCG levels are used to determine the development of postmolar GTN. The diagnosis of postmolar GTN is made when hCG levels plateau for more than three consecutive weeks, or rise for more than two consecutive weeks [1]. Once the diagnosis of GTN is made, ultrasound is one of the imaging tests used for identifying the location and extent of disease. In one study of 33 patients with GTN, ultrasound findings were reviewed and in 17/33 (51.5 %) patients the ultrasound demonstrated uterine disease that correlated 100 % of the time with pathology from an endometrial curettage or hysterectomy. Of the 16/33 patients who did not have evidence of intrauterine disease on ultrasound, the endometrial curettings were positive for fragments of trophoblastic tumor in only 6/16 (37.5 %) [55].

Color Doppler in Diagnosis of GTN

The vascular nature of GTN makes the use of color Doppler in conjunction with TVUS ideally suited for evaluating the presence and extent of intramyometrial disease. The use of Doppler can aid in the identification of myometrial invasion sonographically, a feature of GTN that was previously often only made histologically after hysterectomy. Doppler color flow mapping is seen as abnormal flow through the myometrium in cases of myometrial invasion [20, 28, 51, 56]. TVUS with Doppler can identify small foci of resistant intrauterine disease [29] and can be used to evaluate depth of myometrial invasion which may also be prognostic for resistant disease [34]. Doppler can also be utilized to monitor and measure uterine artery blood flow and a RI and PI can be calculated. In pregnancy the resistance to blood flowing into the uterus drops dramatically with the development of uteroplacental blood vessels and with the hypervascularity of GTD the resistance is even less. In fact, resistive indices progressively decrease as one goes from a nonpregnant uterus, to a normal pregnancy to molar pregnancy to invasive molar pregnancy and choriocarcinoma [27, 57–59]. Thus, in cases where the diagnosis is not clear use of the color Doppler may demonstrate invasion into the myometrium and measurement of uterine artery pulsations may be low suggestive of a diagnosis of GTN.

Ultrasound in the Follow-Up of Molar Pregnancy and GTN

Use in Determining Need for Surgical Intervention

Although the mainstay of treatment for GTN is chemotherapy, in select circumstances surgical intervention is indicated [60]. Ultrasound has proven to be very useful in identifying patients who may benefit from surgery. First, patients presenting with bleeding from persistent intrauterine disease may benefit from a repeat D&C, local resection, or hysterectomy. Second, patients undergoing chemotherapy whose hCG levels indicate chemoresistance may benefit from local resection or hysterectomy, particularly in those women where future fertility is no longer desired [61, 62]. Transvaginal ultrasound with color Doppler should be the first line imaging modality to assess for intrauterine disease when there is concern for heavy vaginal bleeding or drug-resistant uterine tumor.

Uterine Artery Pulsatile Index as a Predictor of Chemotherapy Resistance in GTN

The association of low uterine artery Doppler pulsatile indices and need for chemotherapy has been well established as described above. Thus, several investigators have queried whether the use of these resistive indices might be helpful in identifying patients at risk for chemotherapy resistance. Approximately, 30 % of patients who are considered to have low-risk disease (FIGO risk scores <7) will become resistant to first line single agent chemotherapy and require subsequent alternative chemotherapy [63]. Several studies have demonstrated Doppler indices can be predictive of chemotherapy resistance with patients requiring multi-agent chemotherapy as opposed to single agent chemotherapy having lower resistive indices [34, 64]. Agarwal et al. investigated whether the uterine artery pulsatility index (UAPI) was a predictor of chemotherapy resistance. Initially, they found in 164 patients that those with a UAPI < 1 had 2.68 greater odds of developing methotrexate resistance as opposed to those with inital UAPI > 1 [65]. A subsequent study by the same investigators showed a UAPI < 1 as compared to >1 was predictive of chemotherapy resistance (64.6 % vs. 35.4 %) in multivariate analyses. Patients with a FIGO score of 6 and UAPI $\leq$ 1 had a 100 % rate of single agent methotrexate resistance [66]. Thus, there may be a role for measurement of the UAPI in addition to calculation of the FIGO risk score in patients requiring chemotherapy for GTN.

GTN-Related Arteriovenous Malformations

The development of uterine arteriovenous malformations (AVM) is a well-known complication of GTN. The increased vascularity of the tumor may lead to the creation of abnormal communications between the uterine arteries and the myometrial veins [67]. AVMs can lead to significant life-threatening hemorrhage from the uterus making ultrasound critically important in making the diagnosis and subsequent management. While D&C is the treatment of choice for many conditions with heavy vaginal bleeding, in the case of AVM this could severely exacerbate the bleeding, and other mechanisms for control of bleeding such as hysterectomy or arterial embolization are needed. In order to make the diagnosis sonographically, the Doppler mode is helpful. AVM will demonstrate pronounced vascularity on Doppler ultrasound. Pulse wave Doppler will demonstrate elevated blood flow velocities in both systole and diastole in addition to "spectral broadening reflecting turbulence," low resistive index measurements (between 0.25 and 0.55) and mixing of arterial and venous waveforms [68]. Other investigators have described the hypervascularity of GTN-associated AVM as pale shades during both systole and diastole with a colored mosaic pattern representing the turbulent flow [69]. The AVM may persist long after treatment for GTN is completed. Management for symptomatic (i.e., bleeding) AVM can include selective uterine arterial embolization. The largest series of GTN-associated AVM reported in the literature described 19 cases with successful embolization in 18 of those patients, with 15/18 achieving success after one embolization with polyvinyl alcohol particles. The four remaining patients required two embolization procedures [70]. Successful subsequent normal term pregnancy following embolization treatment for a GTN-associated AVM has been reported in this and another report [70, 71].

Ultrasound for the Evaluation of Subsequent Pregnancies

Vargas et al. reviewed 2432 subsequent pregnancies following complete and partial molar pregnancies and GTN [72]. They demonstrated that patients with a history of molar pregnancy and GTN have similar reproductive outcomes to the general population in subsequent pregnancies, except for observing a 1.7 % incidence of repeat molar pregnancy. Successful pregnancies have even been described following advanced cases of GTN with extensive intrauterine disease that

either caused uterine perforation or required localized resection of the uterus [73]. Therefore, patients should be reassured that following resolution of molar pregnancy and GTN, the vast majority of patients achieve a normal pregnancy. Nonetheless, due to the increased risk of recurrent molar pregnancy, all patients should also undergo a first-trimester ultrasound to rule out repeat molar pregnancy in subsequent gestations.

Teaching Points

- The hydropic villi of complete molar pregnancy give the classic appearance of a "snowstorm" or "cluster of grapes" on ultrasound.
- The sensitivity of ultrasound in the diagnosis of molar pregnancy ranges from 34 to 57 %, which increases dramatically when correlated with the level of hCG.
- Ultrasound is the first-line imaging modality used for the evaluation of the uterus and adnexa in the diagnosis of gestational trophoblastic disease.
- The use of transvaginal ultrasound and color Doppler allows for greater detection of myometrial invasion and persistent uterine disease.
- Uterine artery Doppler indices are significantly lower in GTN than in normal pregnancy.
- Uterine artery Doppler indices can be predictive of persistent disease and chemotherapy resistance.
- Patients with a history of GTD should undergo ultrasound evaluation during subsequent pregnancies to rule out recurrent molar pregnancy.

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Fetal Anomalies

19

Ana Monteagudo, Margaret Dziadosz,
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Introduction

Seek and you shall find.
Matthew 7:7–11

Detection of fetal anomalies using ultrasound (US) has evolved as the US equipment and probes have evolved. The 18- to 20-week anatomy scan has been part of the routine imaging protocol for the pregnant patient for over 25 years; during this scan most fetal anomalies are detected. However, many of the fetal anomalies seen at the 18- to 20-week anatomy scan are present since the first and/or early second trimesters and if looked for can be detected. Bromley et al. [1] reported a 41.4 % detection rates of malformations at 11 to 13 6/7 weeks without even having a dedicated protocol; furthermore, they were able to diagnose 71 % of the lethal anomalies. Becker and Wegner [2] in a prospective observational study to determine the efficacy of the first-trimester anomaly US scanned 3094 consecutive fetuses between 11 and 13 6/7 weeks with an 83.7 % detection rate of major anomalies [2].

High-frequency transvaginal probes have been the mainstay of early fetal anatomical scanning due to their high frequencies and ability to place the transducer close to the developing fetus. The fact that this early scan has been so dependent on the transvaginal scanning modality is, in our opinion, the main reason why first- and early second-trimester fetal anatomical scanning have not gained popularity. Another, important reason is the lack of understanding of early fetal developmental anatomy and the embryology of many fetal anomalies. On the other hand, recent advances in transabdominal imaging have resulted in high-frequency probes that allow imaging of the first- and early second-trimester fetus and can therefore be used by operators not willing to engage in transvaginal scanning.

The "nuchal scan," or nuchal translucency (NT) scan, was introduced in the 1990s, and at present approximately 22 % of commercially insured patients and 8 % of publicly insured patients in the USA have the nuchal translucency scan [3]. The NT scan is performed between 11

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and 13 6/7 weeks obtaining three sonographic parameters: crown-rump length (CRL), nuchal translucency (NT) measurement, and the presence or absence of the nasal bone (NB). Therefore, the timing of this scan is ideal for a first trimester anatomical survey.

What Normal and/or Abnormal Fetal Structures Can Be Reliably Detected at This Gestational Age?

In 1992, Timor-Tritsch et al. [4] described 97 low-risk patients scanned between 9 and 14 weeks using transvaginal sonography (TVS); the aim of the study was to assess at what gestational age fetal structures such as body contours, long bones, fingers, face, palate, feet, toes, and the four-chamber view could consistently be imaged. The study revealed that by 13–14 weeks all of the structures looked for could be consistently imaged (Table 19.1). Whitlow et al. [5] in 1998 performed a study to determine which was the optimal gestational age to measure the nuchal translucency and at the same time examine the fetal anatomy. They concluded that the best time is at 13 weeks of gestation. Important as well is the fact that with increasing gestational age the percentage of the cases in which anatomy could be seen increased from 75 % at 11 weeks to 98 % at 13 weeks; in addition, they noted that as gestational age increased the need for TVS decreased from 42 % at 11 weeks to 15 % at 13 weeks.

In 2004, Souka et al. [6] published on the feasibility of examining cardiac and non-cardiac fetal anatomy in 1144 low-risk women between 11 and 14 weeks. The scan was performed using both transabdominal sonography (TAS) as well as TVS imaging the following anatomical structures: skull, brain, face, spine, four-chamber and three-vessel views of the heart, stomach, abdominal wall, kidneys, bladder, and extremities. The results revealed that a complete anatomy scan was possible in 48 % of the fetuses. Non-cardiac anatomy was successfully imaged in 86 % of the fetuses. The use of TVS increased the successful examination of fetal

Table 19.1 List of embryonic/fetal structures and the gestational age at which they are always seen[a]

Weeks	N	Ant & Post contours	Long bones	Fingers	Face Palate	Foot Toes	4 Chamber view
9	17	+	F&H ± T&R -	±	-	-	-
10	16	+	F&H ± T&R -	±	±	-	-
11	17	+	+	±	±	±	-
12	15	+	+	+	+	±	±
13	14	+	+	+	+	+	±
14	18	+	+	+	+	+	+

± : Threshold level (first seen)

+: Discriminatory level (always seen)

F **femur**, *H* **humerus**, *T* **tibia**, *R* **radius**

[a]Modified from ref. [4]

Table 19.2 Visualization rates of non-cardiac and cardiac structures with increasing CRL[a]

CRL (mm)	Non-cardiac (%)	Cardiac	
		4 ChV (%)	3V (%)
45–54	65	67	25
55–64	84	86	46
65–74	93	93	58
>74	96	97	67

CRL crown-rump length, *4ChV* four-chamber view, *3V* three-vessel view
[a]Based on data from ref. [6]

anatomy from 72 to 86 % of the fetuses. Transvaginal scanning was particularly helpful in examining the face, kidneys and bladder (Table 19.2). Similarly, to other studies they found that as the crown-rump length increased so did the visualization rates of fetal structures.

In 2004, Timor-Tritsch et al. [7] tested the ability of a group of American sonographers to successfully perform fetal structural evaluation 11-14 weeks. The results showed comparable detection rates to those reported by European authors. In their prospective cross-sectional study of 223 women between 11 and 13 6/7 weeks, the sonographers were asked to look for fetal structures of the head, neck, spine, heart, abdomen, chest, and extremities targeted 37 fetal structures (Table 19.3). Cases were divided by gestational age into two groups: 11–12 and 13–14 weeks. Similarly to prior studies, as the gestational age increased the number of structures seen increased as well. In this study, the heart structures had the lowest percentage rate of visualization which is not surprising since most practitioners find the fetal heart to be among the most difficult fetal structures to image. The authors concluded that anatomic survey of the fetus between 11 and 14 weeks can be performed by sonographers with good detection rates of most fetal structures.

In a recent systematic review, Rossi et al. [8] looked at the efficacy of ultrasound between 11 and 14 weeks in the diagnosis of fetal structural malformations. They reviewed 19 articles with 78,002 fetuses undergoing fetal anatomical survey at 11–14 weeks. There were 996 fetuses with malformation with a prevalence of 12 malformations per 1000 fetuses. The overall detection rate of anomalies in this systematic review was 51 %, with detection rates increasing to 62 % when both TAS and TVS were included. Furthermore, the detection rate increased to 65 % among those patients who were at high risk for malformations.

Which Fetal Anatomical Structures Should Be Sought in the Fetal Anatomical Survey at 11 to 13 6/7 Weeks?

Before proceeding, it is important to make one critical clinical important point to keep in mind when scanning the fetus at these gestational ages. ***Gestational age matters***! Not all structures sought during the second trimester (18–22 weeks) scan are completely formed at 11 to 13 6/7 weeks and not all fetal structures "mature" at the same time or at the same gestational age. For example, the fetal brain develops and continually changes during embryonic/fetal life. Depending on the gestational age structures may be deemed normal or pathologic while in reality they did not yet complete their development. For example, in the first trimester a difference of 5–7 days in the gestational age may lead to misdiagnosing a normally developing ventricular structure such as the rhombencephalon as ventriculomegaly or non-visualization of the falx as holoprosencephaly. Therefore, when performing an early fetal anatomical survey, the American Institute of Ultrasound in Medicine (AIUM) [9] list of structures that constitutes a fetal anatomical scan at 18–20 weeks cannot be applied to the fetus at this early gestational age. In 2013 the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) published guidelines [10] as well as a list of suggested structures to be included in the first trimester anatomical survey (Table 19.4).

In this chapter we use the ISUOG list of suggested structures to be imaged at 11 to 13 6/7 weeks (see Table 19.4). Using these guidelines we present fetal anomalies that can be detected at these ages.

Table 19.3 Percentage of structures seen at 11–12 and 13–14 weeks by dedicated sonographers[a]

Structure	11–12 weeks $n=121$ (%)	13–14 weeks $N=102$ (%)	P value
Head and neck			
Calvarium	120 (99)	100 (98)	NS
Intracranial anatomy	115 (95)	97 (95)	NS
Lateral ventricles	109 (99)	94 (92)	NS
Choroid plexus	118 (98)	97 (95)	NS
Cerebellum	63 (52)	70 (69)	0.01
Posterior fossa/cisterna magna	67 (55)	73 (72)	0.01
Nuchal anatomy	115 (96)	95 (93)	NS
Lenses	106 (88)	91 (89)	NS
Profile	110 (91)	91 (89)	NS
Nose/lips	86 (71)	81 (79)	NS
Face	89 (74)	85 (83)	0.08
Spine			
Cervical	97 (80)	91 (89)	NS
Thoracic	98 (81)	89 (87)	NS
Lumbar	87 (72)	79 (77)	NS
Sacral	42 (35)	49 (48)	NS
Heart			
Cardiac axis	86 (71)	75 (73)	NS
4-chamber view	33 (27)	42 (41)	0.03
RVOT	47 (39)	59 (58)	0.04
LVOT	45 (37)	62 (61)	0.0004
Aortic arch	22 (18)	31 (30)	0.03
Ductal arch	18 (15)	24 (24)	NS
Abdomen and chest			
Lungs	77 (64)	79 (77)	0.02
Diaphragm	65 (87)	94 (92)	NS
Ventral wall (cord insertion)	117 (97)	98 (96)	NS
Stomach	118 (98)	100 (98)	NS
Kidneys	97 (80)	93 (91)	0.02
Bladder	113 (93)	92 (96)	NS
2 vessels observed by the bladder	102 (84)	92 (90)	NS
Bowel	93 (77)	90 (88)	0.02
Genitalia	39 (32)	51 (50)	0.007
Extremities			
Humerus	118 (98)	98 (96)	NS
Radius/ulna	115 (95)	99 (97)	NS
Hand	118 (98)	100 (98)	NS
Fingers	104 (86)	92 (90)	NS
Femur	119 (98)	98 (96)	NS
Tibia/fibula	111 (92)	96 (94)	NS
Foot	117 (97)	95 (93)	NS

[a]Reprinted from American Journal of Obstetrics and Gynecology, 191(4), Timor-Tritsch IE, Bashiri A, Monteagudo A, Arslan AA, Qualified and trained sonographers in the US can perform early fetal anatomy scans between 11 and 14 weeks, 1247–52, Copyright 2004, with permission from Elsevier

Table 19.4 Suggested anatomical assessment at time of 11 to 13+6-week scan[a]

Organ/ anatomical area	Present and/or normal?
Head	Present
	Cranial bones
	Midline falx
	Choroid-plexus-filled ventricles
Neck	Normal appearance
	Nuchal translucency thickness (if accepted after informed consent and trained/certified operator available)[b]
Face	Eyes with lens[b]
	Nasal bone[b]
	Normal profile/mandible[b]
	Intact lips[b]
Spine	Vertebrae (longitudinal and axial)[b]
	Intact overlying skin[b]
Chest	Symmetrical lung fields
	No effusions or masses
Heart	Cardiac regular activity
	Four symmetrical chambers[b]
Abdomen	Stomach present in left upper quadrant
	Bladder[b]
	Kidneys[b]
Abdominal wall	Normal cord insertion
	No umbilical defects
Extremities	Four limbs each with three segments
	Hands and feet with normal orientation[b]
Placenta	Size and texture
Cord	Three-vessel cord[b]

[a]Reprinted from Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, et al. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol. 2013;41(1):102–13, with permission from John Wiley & Sons
[b]Optional structures

Head

Exencephaly–Anencephaly Sequence, Cephalocele

Anomalies that result from failure or abnormal closure of the anterior cranial neuropore at around 26–32 days post conception result in cerebral, spinal or a combined cerebral and spinal defects or dysraphia among these exencephaly–anencephaly sequence, cephaloceles, and spina bifida are among the most common defects with a reported prevalence of 1/1000 pregnancies [11].

The exencephaly–anencephaly sequence is a lethal malformation. In exencephaly the typical sonographic features is acrania in which a relatively well formed brain is seen without the covering fetal cranium (Fig. 19.1). As the pregnancy continues the exposed fetal brain begins to disintegrate eventually, resulting in the typical sonographic features of anencephaly in which the cranium is absent and the fetal orbits prominent. Increasing the US gain the amniotic fluid appears speckled as the result of the sloughing off of the exposed brain tissue (Fig. 19.2) [12]. Reported detection rates at 11 to 13 6/7 weeks are 100 % [8, 13].

Cephalocele is a cranial defect that occurs along the bony sutures, through which brain and/or meninges or a combination of both herniates; this defect is thought to occur as a result of faulty cranial mesoderm development. Recent theories suggest that cephalocele is developmentally and genetically different from exencephaly–anencephaly sequence and should not be considered a neural tube defect [11]. Studies on posterior cephalocele occurring in fetuses with Meckel syndrome have found a relationship with ciliopathy syndromes [11]. Sonographic features are sac-like structures posterior to the head in cases of posterior cephalocele or anterior by the fetal face in cases of an anterior cephalocele (Fig. 19.3). The cephalocele may be small or large. They may contain only meninges (meningocele) or brain tissue (meningomylocele). The larger the cephalocele the more brain tissue it contains, the worse is the prognosis for the fetus. Microcephaly may be seen in as many as 20–25 % of the cases. Reported detection rates at 11 to 13 6/7 weeks are 100 % [8].

Holoprosencephaly

During normal fetal development the falx cerebri, a midline structure that separates the single cavity of the forebrain into two hemispheres, should be seen after 9–10 weeks in all normal brains. Lack of visualization of the falx cerebri is consistent with alobar holoprosencephaly (HPE) (Fig. 19.4). At 11 to 13 6/7 weeks the choroid

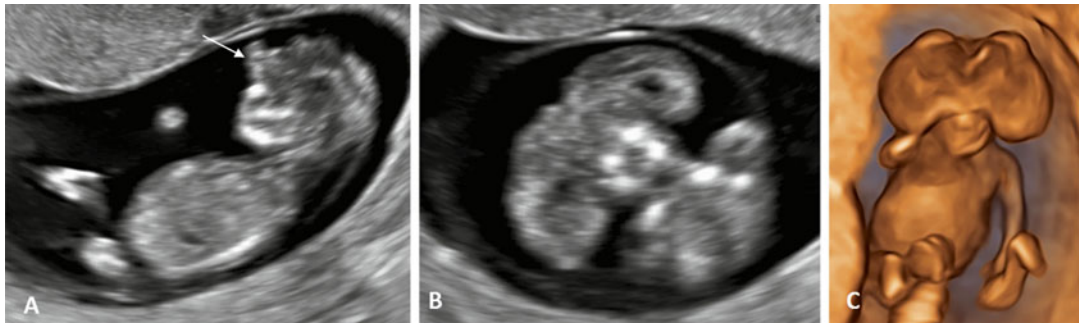

Fig. 19.1 A 10 3/7 weeks fetus with exencephaly–anencephaly sequence. (**a**) Sagittal view: the normal fetal calvarium is not seen; instead the head appears "flat" and irregular. (**b**) Coronal view of the fetal head depicting significant amount of brain tissue that has "drooped" to the side of head since it is not confined by the calvarium. (**c**) 3D reconstruction of the fetus demonstrating exencephaly. (*Arrow*: abnormal head with absent calvarium.)

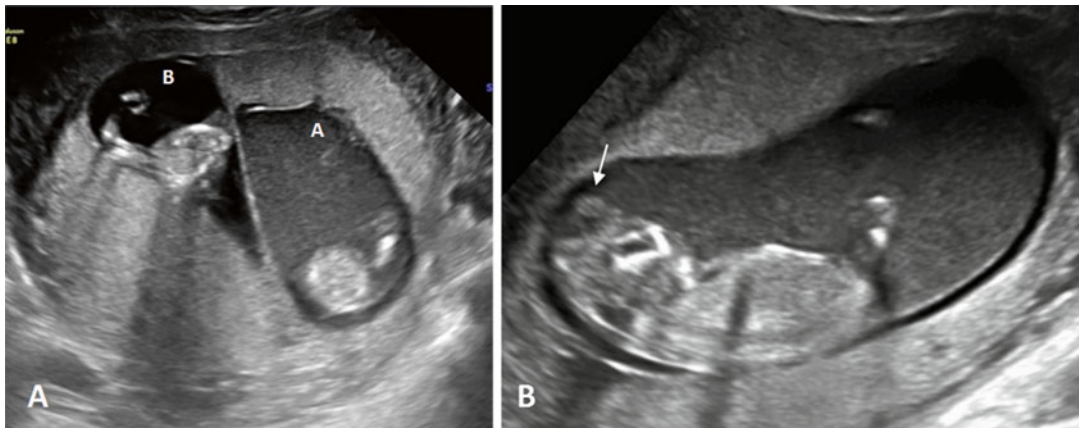

Fig. 19.2 Dichorionic–diamniotic (DCDA) twins at 13 1/7 weeks. (**a**) The amniotic fluid of twin A appears speckled compared to the amniotic fluid of twin *B*. (**b**) Further anatomic evaluation of twin *A* reveals the typical features of the exencephaly–anencephaly sequence; the head appears irregular and lacks the typical sonographic appearance of the smooth and regular echogenic calvarium (*arrow*)

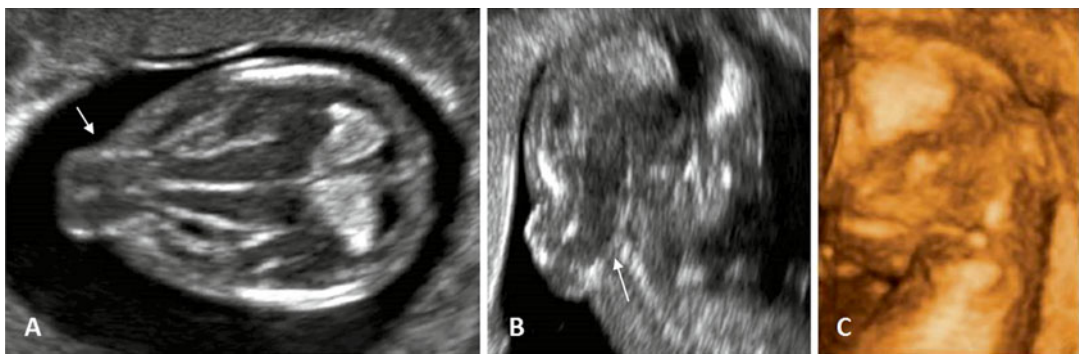

Fig. 19.3 Posterior cephalocele at 12 4/7 weeks. (**a**) Axial section of the fetal head demonstrating the posterior cranial defect through which brain has herniated into the posterior cephalocele sac (*arrow*). (**b**) Sagittal view of the fetal head demonstrating the posterior cranial defect, the cephalocele sac with the brain and midbrain herniating into the sac (*arrow*). (**c**) 3D reconstruction of the cephalocele

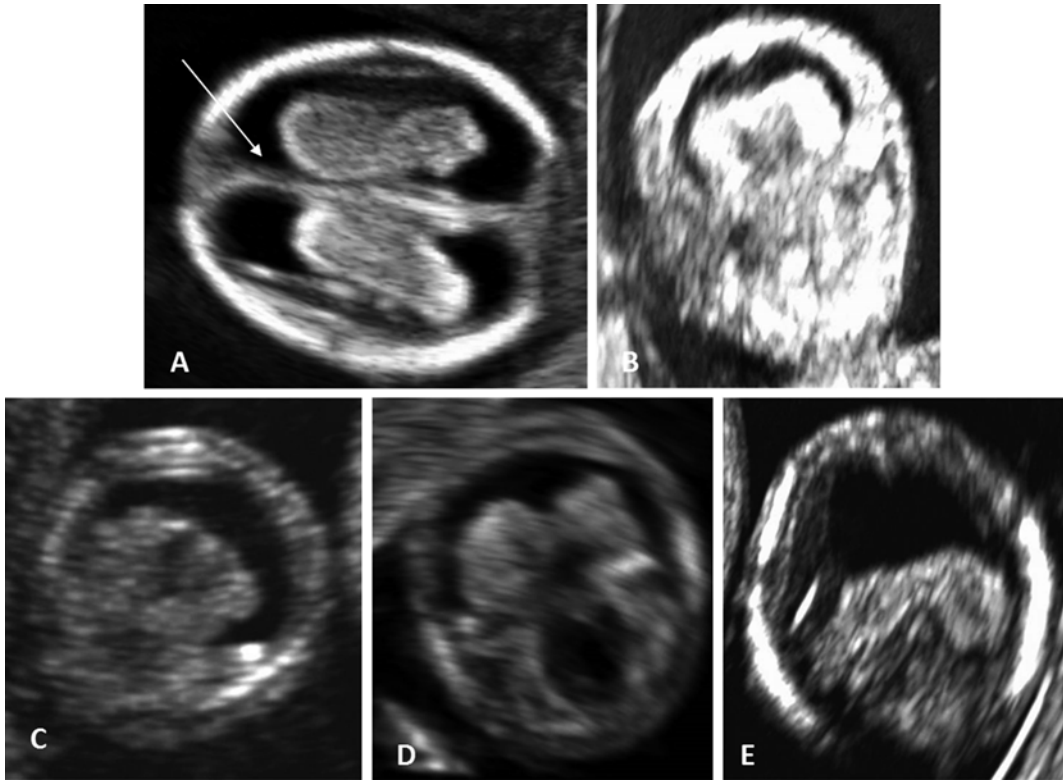

Fig. 19.4 A composite image of a normal brain and four cases of holoprosencephaly. (**a**) Axial section of a normal fetus at 13 2/7 weeks for comparison, displaying the midline falx cerebri which divides the brain into the right and left hemispheres; the echogenic choroid plexus is seen to each side of the falx (Arrow=Falx). This appearance has been likened to a butterfly with open wings. (**b**) Fetus with HPE at 9 6/7 weeks. (**c**) Fetus with HPE at 11 4/7 weeks. (**d**) Fetus with HPE at 12 1/7 weeks. (**e**) Fetus with HPE at 13 2/7 weeks. The common sonographic feature of all four fetuses with holoprosencephaly imaged in an axial view is the absent falx; single ventricular cavity; choroid plexus superior to the fused thalami; and absence of the normal "butterfly" appearance of the axial view

plexus is seen on each side of the midline falx; this configuration has been likened to a butterfly with the wings open [14] (see Fig. 19.4a). Using the "butterfly sign" Sepulveda et al. [15] screened 11,068 live fetuses for HPE over a 9-year period. Among this cohort they diagnosed 11 cases of HPE, which demonstrated lack of visualization of the "butterfly sign." Detection rate of HPE using the absent "butterfly sign" was 100 %. In addition, they noted that 40 % had a biparietal-diameter less than the fifth centile for gestational age (GA); which further aided in the diagnosis.

Holoprosencephaly is a common malformation involving the forebrain; this malformation results from complete or incomplete failure of the forebrain to divide during the second to the third week post-conception [16–18]. The prevalence of holoprosencephaly at 11 to 13 6/7 weeks has been reported as 1:1300 pregnancies; with approximately 66 % having a chromosomal abnormality of which 86 % have trisomy 13 and 4 % trisomy 18 [19]. This anomaly has a spectrum ranging from the most severe alobar HPE, to semilobar HPE, and to lobar HPE and the least severe middle interhemispheric variant (MIHV). In approximately 80 % of individuals affected with HPE [9] a craniofacial anomaly is also present [16]. The craniofacial anomalies range from cyclopia (single midline eye), synophthalmia (partial midline face fusion of the two eye), and a proboscis (nasal appendage with a single nostril located above the eyes) [17]. During the first

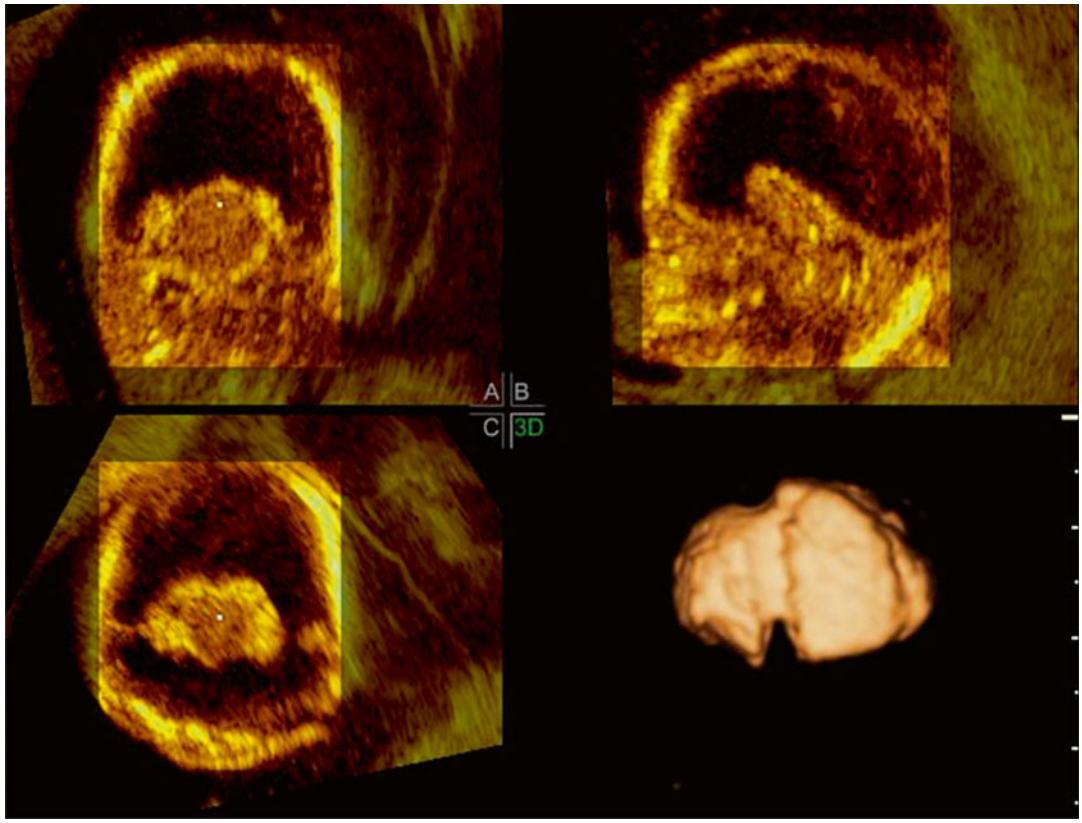

Fig. 19.5 Three-dimensional display of the three orthogonal scanning planes (axial, coronal, and sagittal) as well as the inversion mode; in which the anechoic cerebral spinal fluid is "inverted" and displayed as an echogenic structure in a fetus with trisomy 13 at 13 5/7 weeks with alobar HPE. (**a**) Coronal section showing the single or "mono" ventricle; absence of the midline structures and fused thalami. (**b**) Sagittal view of the fetus; the face is facing the left side of the picture; the head contains fluid. (**c**) Axial section showing similar features described in (**a**). *Box* 3D depicts the inverted image of the fluid contained within the single brain ventricle

trimester, most of the cases of HPE that are diagnosed are alobar; although the semilobar type can also be diagnosed; however, at 11 to 13 6/7 weeks, this presents a challenging task. Three-dimensional inversion rendering can be used to differentiate between a normal brain and HPE; this can be used as an additional tool in the diagnosis of HPE in the first trimester [20] (Fig. 19.5). Lobar HPE, which is a more subtle malformation and depends upon the appearance of the cava is diagnosed at or after the 18- to 20-week anatomy scan. Most fetuses affected by HPE do not survive. Detection rates of 50–100 % have been reported [8, 13].

Neck

Thickened Nuchal Translucency and Cystic Hygroma

The significance of thickened or increased nuchal translucency (NT) in the screening for aneuploidies, congenital heart defects and other malformations is well established. Thickened NT refers to a measurement that is greater than the 95th centile; which in turn increases with gestational age and is just about 2.5 mm; in contrast, its 99th centile is fixed at 3.5 mm (Fig. 19.6) [21, 22]. A thickened NT in itself is not an abnormality since it can be seen in both normal pregnancies as well

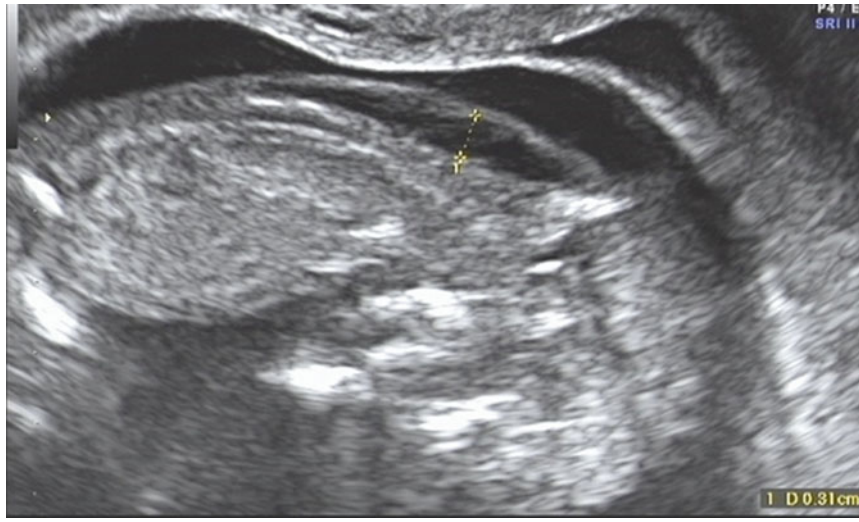

Fig. 19.6 Fetus at 11 5/7 weeks demonstrating NT of 3.1 mm; at this gestational age this measurement falls above the 95th centile

as those with pathologies. Kagan et al. [23] looked at the relationship between thickened NT and chromosomal defect. With increasing NT from the 95th centile to 3.4 mm the incidence of chromosomal aneuploidy was 7 %; at an NT of 3.5–4.4 mm the incidence of chromosomal aneuploidy was 20 %; at a NT of 4.5–5.4 mm it was 45 %; at a NT of 5.5–6.4 mm, 50 %; at a NT of 6.5–7.4 mm, 70 %; and with NT of ≥8.5 mm, 75 %. Another interesting finding was that about half of the fetuses with trisomy 21 has NTs ≤ 4.5 mm; NT greater than 4.5 mm was seen in about 60 % of the cases with trisomy 13, 75 % of fetuses with trisomy 18 and 90 % of cases of Turner syndrome; moreover, fetuses with Turner tended to have the thickest NT ≥ 8.5 mm.

In euploid fetuses with thickened NT the association with congenital heart defects (CHD) is well known. In a 2003 meta-analysis by Makrydinas et al. [24] an NT > 95th centile had a sensitivity of 37 % and specificity of 96.6 %; and for NT > 99th centile they were 31 % and of 98.7 %, respectively, with a positive likelihood ratio of 24 for the diagnosis of major congenital heart defect [21, 24]. In a subsequent 2013 meta-analysis by Sotiriadis et al. [25] they found that approximately 45 % of chromosomally normal fetuses with CHD had an NT > 95th and 20 % had an NT > 99th centile.

Cystic hygroma refers to bilateral, septated, cystic, fluid-filled spaces located in the occipitocervical region [26]. This is a result of obstruction between the lymphatic and venous vessels in the neck resulting in accumulation of lymph in the jugular lymphatic sacs (Fig. 19.7). In fetuses with cystic hygroma between 11 and 13 6/7 weeks approximately 51 % [27] to 54.9 % [28] will have a chromosomal abnormality; of which trisomy 21 is the most common. In a recent retrospective cohort study of 944 fetuses with first trimester cystic hygroma; the prevalence of trisomy 21 was 21.4 %; followed by monosomy X (Turner syndrome) 12.1 %, trisomy 18 at 11.4 % and trisomy 13 at 3.6 % and other karyotypic abnormalities such as other trisomies, deletions, duplications, unbalanced translocations, inversions, and sex chromosome abnormalities [28]. Among the fetuses with normal karyotype 28.8 % had a major anomaly. Urinary, central nervous system, and cardiac were the most common accounting for 15 % of the anomalies [28]. In the same cohort six fetuses had genetic syndromes; Angelman and Noonan syndrome were among the genetic syndromes seen. Perinatal loss

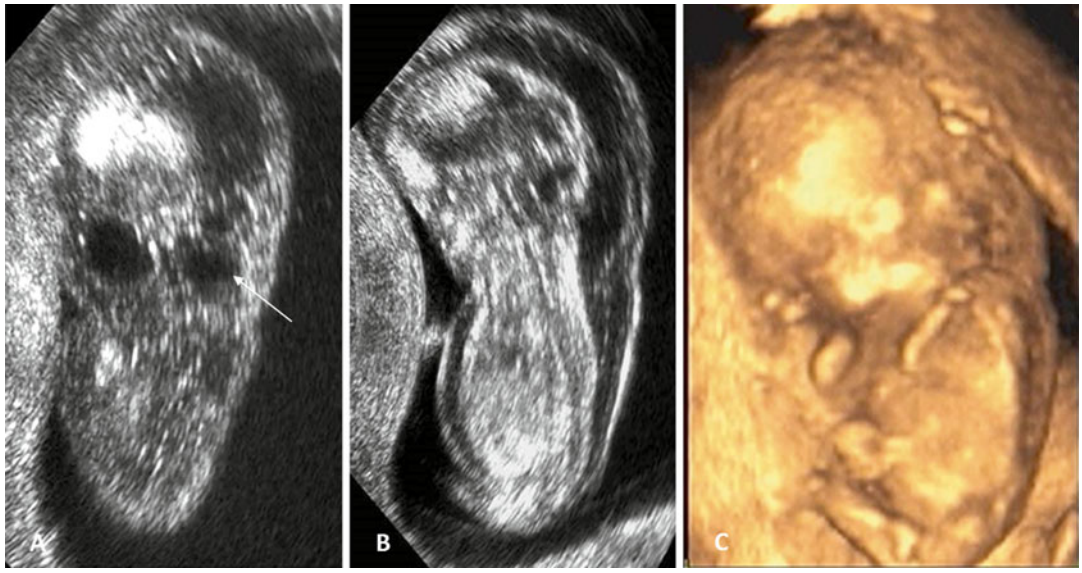

Fig. 19.7 Fetus at 12 3/7 weeks with cystic hygroma. (**a**) Posterior coronal section showing the bilateral cystic dilatation at the level of the posterior neck area (*arrow*). This pathology is a result of obstruction between the lymphatic and venous vessels in the neck resulting in accumulation of lymph in the jugular lymphatic sacs. (**b**) Sagittal view of the fetus showing extensive posterior hygroma and the total body edema. (**c**) 3D reconstruction of cystic hygroma

occurred in 39 % of ongoing pregnancies and the overall abnormal outcome ensued in 86.6 % of the fetuses [28].

Face

Absent Nasal Bone, Cleft Lip ± Palate, Cataracts, Micrognathia

During the early anatomical survey, similarly to the traditional second trimester anatomical survey, a profile view of the face should be obtained. This may reveal an absent or hypoplastic nasal bone, a cleft lip and/or palate, or micrognathia.

Absent nasal bone is not a fetal malformation per se however it is a marker of fetal aneuploidy; specifically of the common trisomies (Fig. 19.8). The nasal bones are actually paired structures, there is a right and a left nasal bone, and there can be unilateral as well as bilateral absence or hypoplasia. Absent nasal bone is seen in 60 % of fetuses with trisomy 21, 53 % of trisomy 18 and in 45 % of trisomy 13; its absence confers a likelihood ratio of 27.8 for Down syndrome; furthermore, it can be seen in 2.5 % of euploid fetuses [29]. Among euploid pregnancies absent nasal bone is seen more frequently in African American women (5.8 %) than in white women (2.6 %) or Asian women (2.1 %) [30]. In a recent publication among 57 fetuses with absent nasal bone and normal karyotype three fetuses had an adverse outcome and, in all, additional sonographic abnormalities were seen [30].

Cleft lip and/or palate (*CLP*) is a common facial anomaly with a reported incidence of 1.7 per 1000 live births; however, ethnic and geographic variation exist [31]. In up to 80 % of the cases cleft lip is unilateral, typically affecting the left side and most of the affected fetuses are male. However, isolated cleft palate is more commonly seen in females with a reported incidence of 1 in 2500 live births [31]. During development, a continuous upper lip is formed by 8 weeks when the medial nasal and maxillary processes fuse. Failure of fusion of the medial nasal and maxillary processes will result in a cleft lip affecting one or both sides. The palate develops from the primary and the secondary palate. Its development starts at 7 weeks, but is not completed until the 14th week.

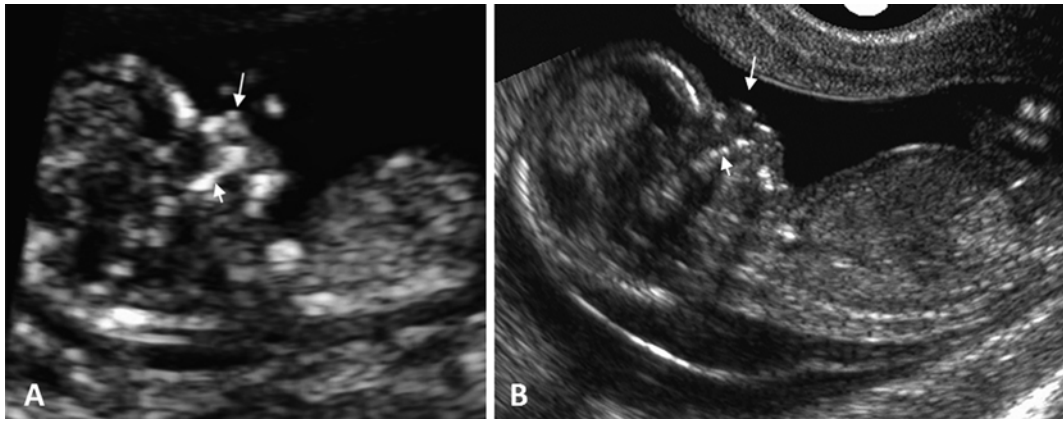

Fig. 19.8 Two fetuses are seen, one with a normal and one with absent nasal bone and cystic hygroma. To image the nasal bone or its absence it is important to obtain the correct sagittal scanning plane of the face which shows the tip of the nose (*long arrow*) and the palate (*short arrow*). (**a**) Fetus at 12 1/7 weeks with a normal-appearing nasal bone. (**b**) Fetus with absent nasal bone at 13 6/7 weeks

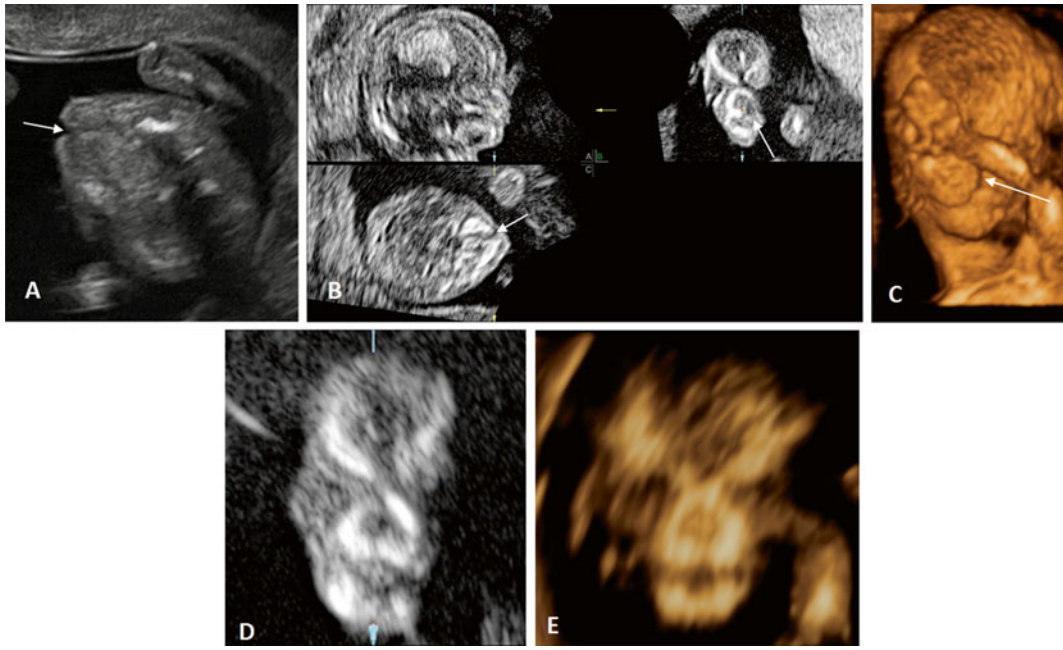

Fig. 19.9 Fetus with unilateral left-sided cleft lip and palate at 12 5/7 weeks. (**a**) Axial section through the upper lip of a fetus with unilateral cleft lip and palate diagnosed at the time of the nuchal translucency scan (*arrow*). (**b**) 3D orthogonal planes of the same fetus. *Box A*: a sagittal view of the face. Upper Left *Box B*: a coronal section showing the abnormal retronasal triangle with a gap at the area of the left side of the palate (*arrow*). Lower Left *Box C*: the axial section; *arrow* points to defect (**c**) 3D reconstruction of the fetus with the unilateral cleft lip and palate (*arrow*). (**d**, **e**) 2D and 3D thick slices of a normal retronasal triangle

At 11 to 13 6/7 weeks a sagittal, coronal, and axial view using 2D and 3D sonography can detect a CLP (Fig. 19.9). In cases of bilateral cleft lip and palate a protuberance is seen anterior to the lips in the sagittal plane; in the axial plane the cleft lip and palate can be seen as a deep indentation. Three-dimensional ultrasound, specifically 3D reconstruction of the face using the coronal plane

can help in evaluating the facial defects (see Fig. 19.9b). Detection rates of CLP in the first trimester are low, ranging from 5 to 50 % [8, 13]. The retronasal triangle (see Fig. 19.9e) can be imaged, using 2D or 3D sonography, by obtaining an anterior coronal view of the fetal face. The apex of the retronasal triangle is made up of the two nasal bones, the sides are the frontal process of the maxilla and the base of the triangle is the primary palate [32]. In cases of CLP, a defect can be imaged at the base of the triangle, at the site of the palate (Fig. 19.9b Box C) Boc C. The retronasal triangle view likely can improve the detection and diagnostic rates of CLP; however, no large prospective studies looking at efficacy of the retronasal triangle are available to date. Furthermore, this view has recently been reported as a new way to evaluate the presence or absence of the nasal bones [32–34].

Cataracts: the reported incidence is 1–6/10,000 births [35]. The fetal lens develops from the surface ectoderm before the sixth week of gestation [35]. Fetal cataracts may be the result of a very early in-utero fetal infection, such as rubella, varicella, herpes and CMV, exposure to a toxin (anti-psychotic drugs such as carbamazepine), idiopathic or genetic. A genetic cause is seen in 30 % of unilateral cases and in 50 % of bilateral cases [35]; genetic causes includes syndromes such as Walker–Warburg syndrome and karyotypic abnormalities such as trisomy 21, 18, and 13. The normal sonographic appearance of the fetal lens is that of a ring with an anechoic center and an outer echogenic rim (Fig. 19.10a). At times the hyaloid artery can be seen as a linear structure between the posterior aspect of the lens and the optic disc; however, the hyaloid artery typically regresses before birth. In fetal cataracts there is opacification of the anechoic center-core of the lens; at times, in conjunction with cataracts, there may be reduction in the size of the fetal eyes [36] (see Fig. 19.10b).

The mandibular process forms the lower jaw, lip and chin at around 8–12 weeks; with final fusion of all of the parts that will form the mandible completed by 13 weeks of pregnancy. Normal development of the mandible can be disrupted as the result of genetic syndromes or

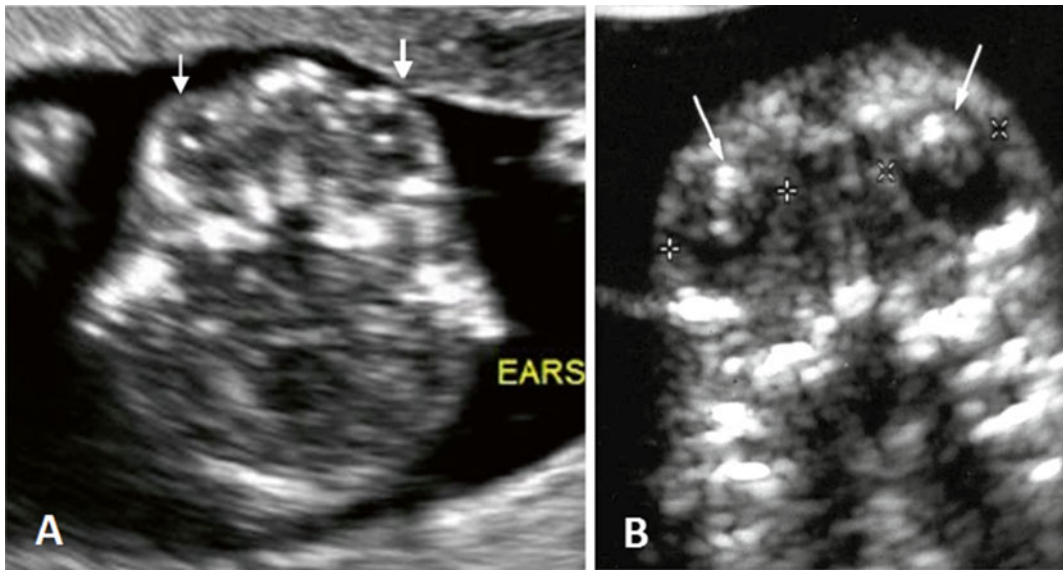

Fig. 19.10 Axial section of the fetal face at the level of the fetal orbits. (**a**) Normal fetus within the orbits the normal lenses are seen. The sonographic appearance of a normal lens is that of an echoic ring with a central sonolucency (*arrows*). (**b**) Axial section of a fetus with autosomal dominant cataracts at 12 5/7 weeks. Within the normal orbits, the ring-like appearance of the lens is lost and replaced by a ring filled with a central echogenic material, the cataract. The *arrow* points to the small and receding jaw

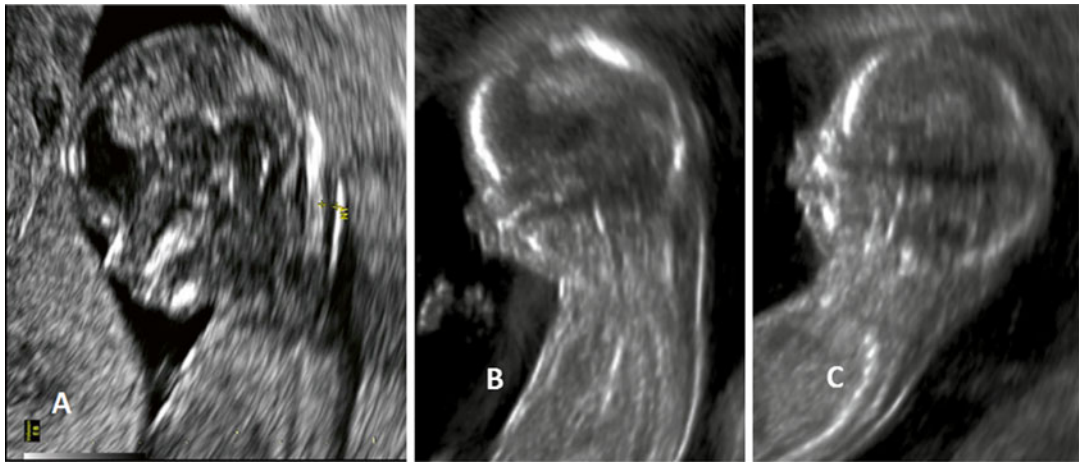

Fig. 19.11 Sagittal view of the fetal profile. (**a**) Normal fetal profile. (**b**, **c**) Slightly different views of the profile of a 13 6/7 weeks fetus with micrognathia and a thick NT. The fetus was a carrier of an unbalanced deletion (arrow=jaw)

environmental exposures [37]. *Micrognathia* is a common feature of over 100 genetic conditions such as Treacher Collins, Robin sequence, fetal akinesia syndrome, and chromosomal aneuploidy such as Trisomies 18 and 13 as well as deletions [37, 38]. As stated by Paladini in 2010 [37] fetal micrognathia is almost always an ominous finding; therefore, when seen, a detailed work up is essential. Using 2D and 3D US, the normal fetal mandible can be imaged in the sagittal plane when obtaining the profile, in an axial view at the level of the mandible or as part of the 3D image of the face (Fig. 19.11a). The diagnosis of micrognathia can rely on subjective assessment or using objective methods such as the jaw index and inferior facial angle. When applying these indexes to fetuses at 11 to 13 6/7 weeks, it is important to remember that they were developed based on fetuses at 18–20 weeks and have not been validated to be used at an earlier gestational age [37, 38] (see Fig. 19.11b).

Spine

Open Spina Bifida

At 11 to 13 6/7 weeks the fetal spine can be assessed in the sagittal, coronal, and axial planes in a similar fashion as it is routinely performed later during the second-trimester anatomical survey. In the second trimester the diagnosis of open spina bifida relies on several sonographic markers: (1) the presence of a bulge or irregularities of the spine; (2) two established and sensitive cranial findings the "lemon sign" and "banana sign." *Open spina bifida* can be diagnosed at 11 to 13 6/7 weeks or earlier by observing a bulge or disruption of the bony spine and skin in the sagittal plane (Fig. 19.12a, b) [39, 40]. The sonographic detection of the "banana and lemon" signs has been reported in fetuses after the 12th week of pregnancy [39, 41]. In pregnancies 12 weeks or less, the cerebellum may just appear slightly convex; but the typical appearance of the "banana sign" can be consistently demonstrated after the 12th week [41]. Recent research in this area has resulted in several additional cranial sonographic findings that have been developed specifically to screen fetuses at 11 to 13 6/7 weeks, especially open spina bifida. The signs include: non-visualization of the intracranial translucency (IT) [42] (see Fig. 19.12c, d), increasing brain stem diameter to brain-stem-to-occipital bone distance (BS/BSOB) [43] and cisterna magna width<5th [44]; as well as in the axial plane the biparietal diameter (BPD) measurement of <5th centile [45, 46] and biparietal-to-transverse abdominal diameter ratio of ≤1 (BPD/TA) [47]. Fetuses "screen positive" for these new cranial sonographic markers should be referred to centers with expertise in scanning the early pregnancy. Most of these new

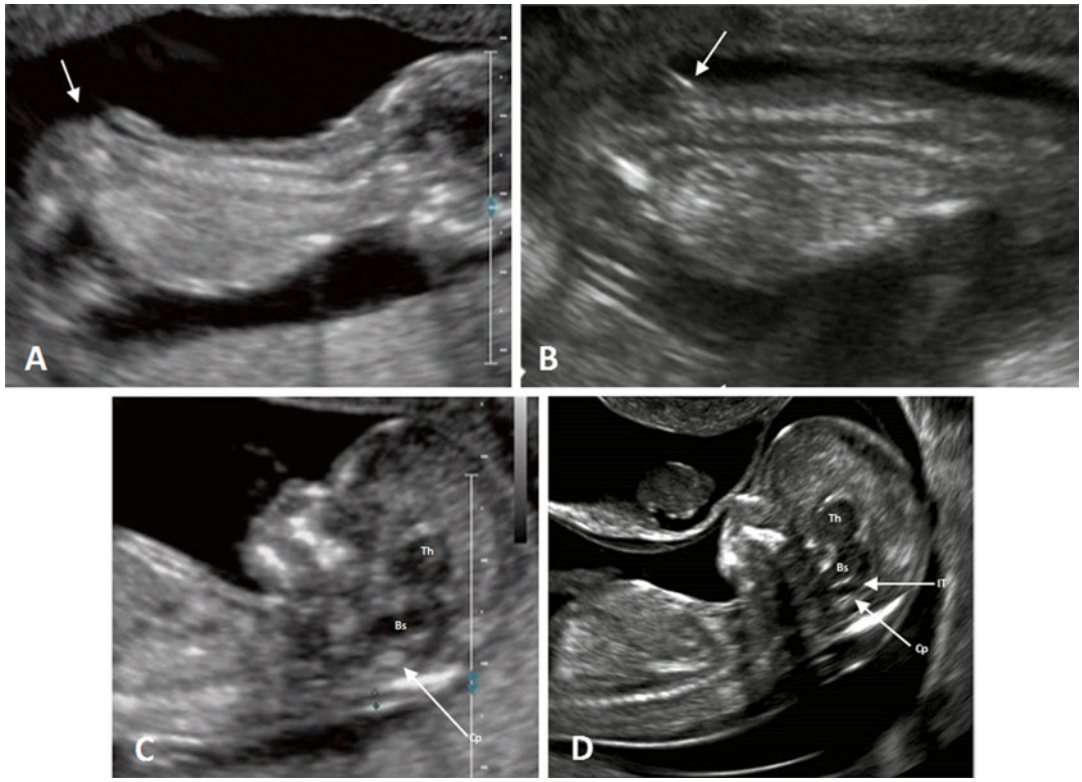

Fig. 19.12 Sagittal image of the fetal spine in at 12 3/7 weeks with a lumbosacral open spina bifida. This finding was confirmed during subsequent studies as well as postnatally. (**a**) The lumbosacral spinal defect is seen at the *arrow*. (**b**) Sagittal view, slightly off the midline, demonstrating the myelomeningocele sac as well as the defect of the vertebral bodies. (**c**) Sagittal view of the fetal head demonstrating lack of visualization of the intracranial translucency. (**d**) Sagittal view of a normal fetus demonstrating the normal intracranial translucency (IT). The IT is seen between the brainstem (Bs) and the choroid plexus (Cp). Th = thalamus

cranial sonographic signs can be looked for in the median view of the fetal face, the same plane used to measure the nuchal translucency. At present, there is limited data regarding the performance of these new cranial signs for the detection of open spina bifida; however, Bernard et al. [45] reported that using a BPD of <5th percentile could detect 50 % of the cases of open spina bifida by selecting about 5 % of the cases for further expert scanning.

Heart

The Abnormal Heart

Congenital heart defect (CHD) is a common anomaly with a reported incidence of 8–10/1000 live births [48]. Currently, detection rates of CHD in the first trimester remain relatively low with the exception of several centers with expertise in first trimester fetal echocardiography. There are many factors that play a significant role in the detection of heart anomalies such as experience in fetal echocardiography, maternal body habitus, equipment quality, and liberal use of transvaginal sonography. The association between a *thickened NT* and CHD is well documented in the literature and was touched on before [21, 24]. In a recent meta-analysis [25] the pooled sensitivity, specificity, LR+, and LR− for NT > 95th was 44.4, 94.5, 7.49, and 0.63 and for an NT > 99th it was 19.5, 99.1, 21, and 0.83, respectively. Of lately, the abnormal ductus venosus flow and tricuspic regurgitation have emerged as important additional sonographic clues when screening for congenital

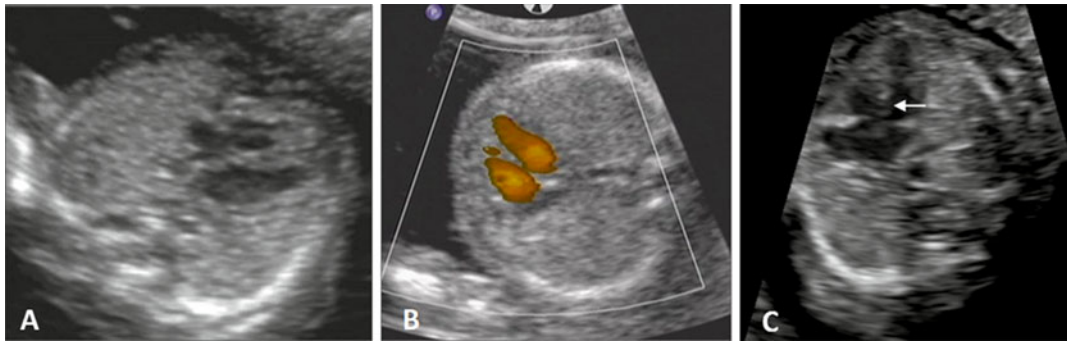

Fig. 19.13 Four-chamber view of the fetal heart. (**a**) Normal four-chamber view of a fetus at 13 3/7 weeks. (**b**) Four-chamber view with power Doppler applied showing normal blood flow through both atrioventricular valves. (**c**) Fetus at 13 weeks with the suspected diagnosis of atrioventricular canal (AV canal) or atrioventricular septal defect (AVSD) defect (*arrow*); the crux of the heart appears abnormal and the two valves cannot be clearly identified

heart defects at 11 to 13 6/7 weeks. In a recent prospective study, *reversed a-wave* in the ductus venosus was seen in 28.2 % of fetuses with CHD compared to 2.1 % of fetuses with no cardiac disease. When both reverse a-wave and NT > 99th centile were present, CHD was seen in 38.8 % and for NT > 95th centile 47.1 % [49]. In a publication from 2011 t*ricuspid regurgitation* was seen in 32.9 % of euploid fetuses with cardiac disease and 1.3 % of fetuses with no cardiac disease; any one of the three markers (thick NT, reversed a-wave, tricuspid regurgitation) was seen in 57.6 % of fetuses with CHD and in 8 % of fetuses without cardiac disease [50]. Among the cardiac anomalies that can be detected after fetal echocardiography in the first trimester are hypoplastic left heart, double outlet right ventricle, and tetralogy of Fallot; detection rates ranges from 50 to 99 % [8] (Fig. 19.13).

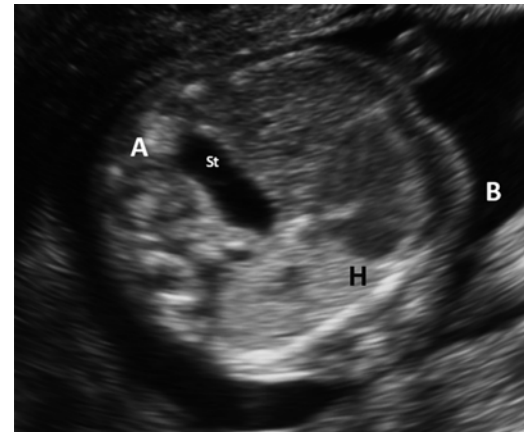

Fig. 19.14 View of the fetal chest at the level of the four chambers; the heart is seen pushed to the right side of the image and in the left side the fetal stomach St is seen. The fetal stomach should never be seen at the same time as the four chambers of the heart (H)—when this is seen the diagnosis is CDH until proven otherwise

Chest

Congenital Diaphragmatic Hernia

When evaluating the fetal chest in the first trimester, symmetry of the lung fields and absence of effusions or masses are the key markers of a normal chest. The normal heart is nestled between the lungs, the apex points to the left and approximately two-thirds of the heart is in the left side of the chest (see Fig. 19.13a, b). When the normal position of the heart is disrupted and the heart is pushed either to the right or left, the presence of a chest mass must be entertained. In *congenital diaphragmatic hernia* the fetal stomach and/or bowel is seen in the chest in the transverse section of the chest (Fig. 19.14). The heart and the mediastinum may be minimally or significantly displaced laterally to the right or the left chest depending on the side of the diaphragmatic

defect. The reported prevalence of congenital diaphragmatic hernia (CDH) is 1 in 2500 to 1 in 3500 live births; with hernias involving the left diaphragm more common than right-sided, with a ratio of 6:1 [51]. Although bilateral hernias have been reported, they are fatal [51]. In 90 % the defect is posterolateral (Bochdalek hernia), 9 % anterior-medial (Morgagni hernia) and the remainder encompasses unusual forms of diaphragmatic defects [51]. In nearly 40 % of the fetuses with CDH, an increased nuchal translucency is seen between 11 and 13 6/7 weeks; the increase in NT may be an early sonographic sign of intrathoracic compression-related pulmonary hypoplasia [52]. Diagnosis of CDH at 11 to 13 6/7 weeks is challenging and even when the NT is increased, detection rates are about 50 % [13]. At present most CDHs are diagnosed later in pregnancy and small defects may only be diagnosed postnatally.

Megacystis

Megacystis is defined as a longitudinal diameter of the fetal bladder of ≥7 mm [19] (Fig. 19.15). In the study of Kagan et al. [19], the reported prevalence at 11 to 13 6/7 weeks was 1:1632 pregnancies, with an incidence of aneuploidy of 31 %. Among the chromosomal aneuploidies, Trisomies 13 and 18 were the most commonly seen abnormality, accounting for 54.5 % and 36.4 %; trisomy 21 was seen in 9.1 % of the cases [19]. Among the majority (68.6 %) of euploid fetuses with megacystis, the bladder was ≤15 mm and spontaneous resolution occurred in 90 % by 16 weeks, resulting in healthy newborns. In two cases there was progression to obstructive uropathy. There were four cases with megacystis with the bladder measuring more than ≥15 mm and these pregnancies were terminated. Megacystis is a relatively easy diagnosis in the first trimester and 100 % detection rates have been reported [13].

Abdomen

Kidneys

The normal fetal kidneys can be imaged at 11 to 13 6/7 weeks. In 2004, our group reported on visualization rates of different fetal structures on scans performed by sonographers [7]. Visualization rates of the normal kidneys and bladder at 11–12 weeks was 80 % and 93 %, respectively; and at 13–14 weeks, 91 % and 96 %, respectively. The normal kidneys at this gestational age appear relatively hyperechoic when compared to the sonographic appearance of kidneys later in the pregnancy. By using color/power Doppler to visualize the renal arteries, one can enhance finding and imaging of the kidneys at this gestational age. The adrenal glands at this gestational age are relatively large, compared to the neighboring kidneys and sonographically are anechoic, as they are also later in pregnancy. Diagnosis of unilateral or bilateral renal agenesis is a difficult diagnosis with detection rates of <20 % in the first trimester [13].

Abdominal Wall

Gastroschisis, Omphalocele, Limb-Body Wall Complex, OEIS (Omphalocele–Exstrophy–Imperforate Anus–Spinal Defects), Pentalogy of Cantrell

Gastroschisis is an abdominal wall defect, typically to the right of the umbilical cord through which herniation of intestinal organs occur (Fig. 19.16). Gastroschisis can be reliably diagnosed at 11 to 13 6/7 weeks with reported detection rates of 50–100 % [8, 13]. Nuchal translucency >95th centile has been reported in approximately 10 % of the cases [13]. In a recent international study [53], approximately 85 % of the cases of gastroschisis were isolated defects; chromosomal syndromes were seen in 1.2 %, with Trisomies 18, 13, sex chromosomes and trisomy 21 being the most common.

Omphalocele is a midline abdominal wall defect, at the level of the umbilical cord insertion into the abdomen, through which bowel alone or bowel and liver herniate into a peritoneal sac

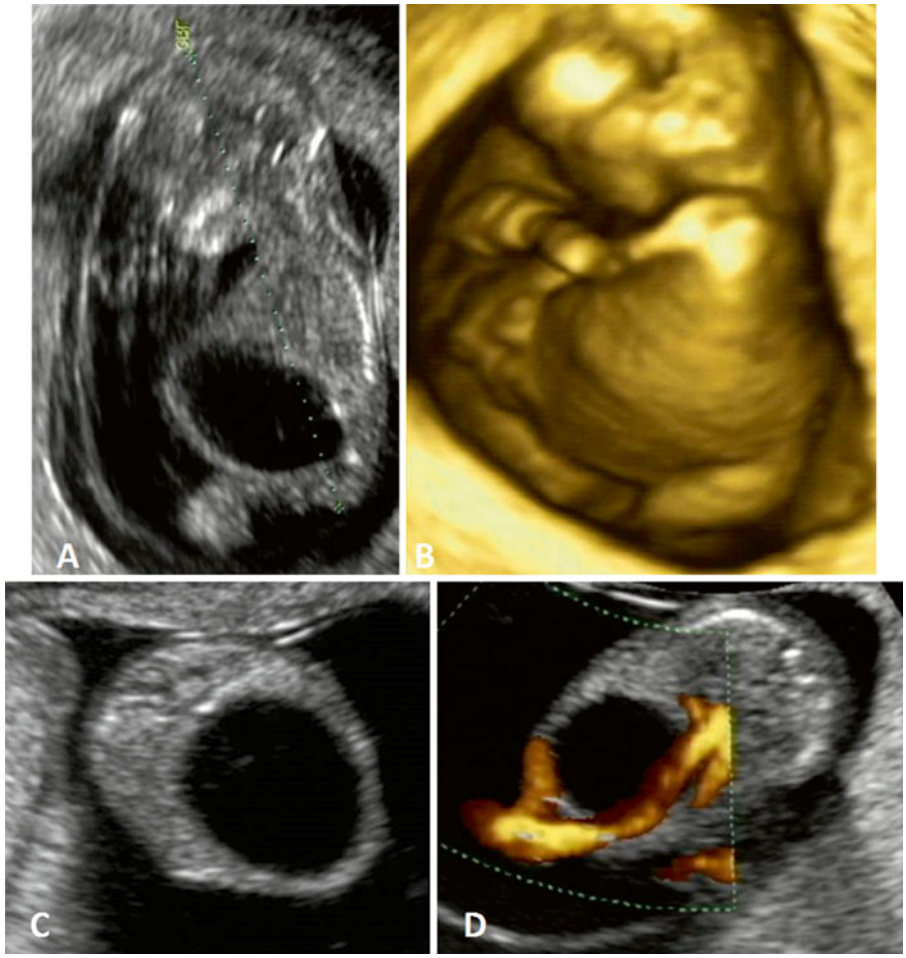

Fig. 19.15 Fetus with megacystis at 12 4/7 weeks. (**a**) On the sagittal view the megacystis is seen filling the fetal pelvis extending into the abdomen. (**b**) A 3D reconstruction of the fetus with megacystis. (**c**, **d**) Transverse section at the level of the large bladder; using power Doppler demonstrates the two umbilical arteries flanking the bladder confirming the diagnosis

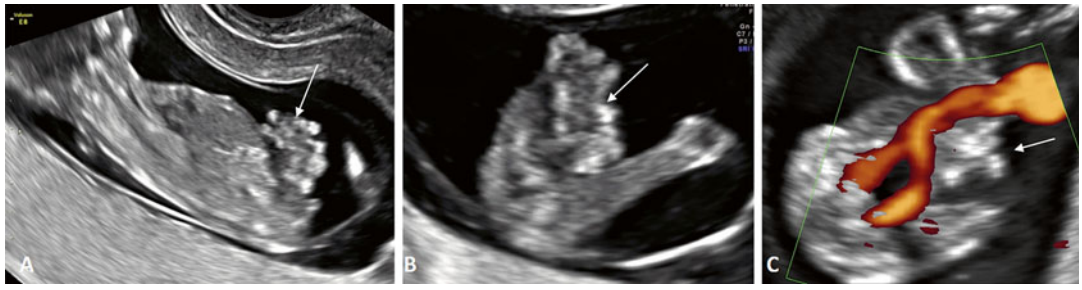

Fig. 19.16 Fetus at 13 0/7 weeks with gastroschisis. (**a**) Sagittal view showing the free floating bowel in the lower abdomen (*arrow*). (**b**) Transverse view at the level of the abdominal wall defect clearly demonstrating the free loops of bowel anterior to the abdomen (*arrow*). (**c**) Using power Doppler the two umbilical vessels are seen, to the right of the umbilical cord insertion the bowel is seen outside the abdominal cavity (*arrow*)

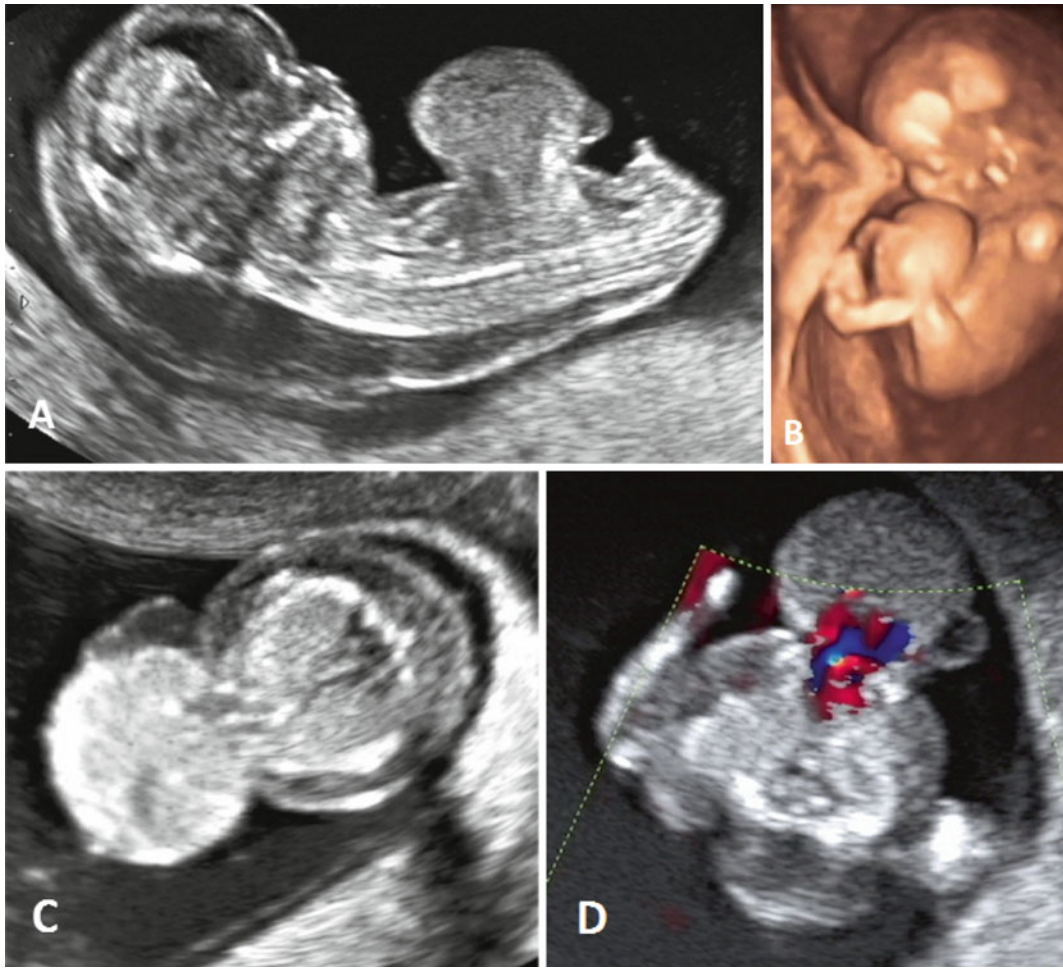

Fig. 19.17 Fetus at 12 5/7 weeks with a large liver-containing omphalocele and a cystic hygroma. (**a**) Sagittal view of the fetus showing the large liver-containing omphalocele. (**b**) 3D rendering of the omphalocele. (**c**) Transverse view through the abdomen at the level of the omphalocele. (**d**) Using color Doppler the fetal heart is seen "pulled inferiorly" almost through the abdominal defect into the omphalocele sac

(Figs. 19.17 and 19.18). The bowel-containing omphalocele can be reliably diagnosed only after the 12th week of the pregnancy. This is due to the fact that the omphalocele containing bowel only may be difficult to differentiate from the physiologic midgut herniation which occurs between 8 and 11 weeks. A pathology has to be considered only after failure of the physiologically herniated bowel loops to return to the abdomen. It is important to note that upwards of 20 % of fetuses do not complete this physiologic replacement as late as 12 completed weeks. This delay is seen more frequently in aneuploid gestations [54].

In a large screening study at 11 to 13 6/7 weeks, the incidence of bowel-containing omphalocele was dependent on the CRL with a prevalence of 1:98 for a CRL of 45–54.9 mm; 1:798 for a CRL of 55–64.9 mm to 1:2073 for CRL 65–84 mm [19]. In our opinion, the high incidence of bowel-containing omphalocele at the smaller CRLs is due to the fact that cases of physiologic midgut herniation were called omphalocele. In contrast, the prevalence of

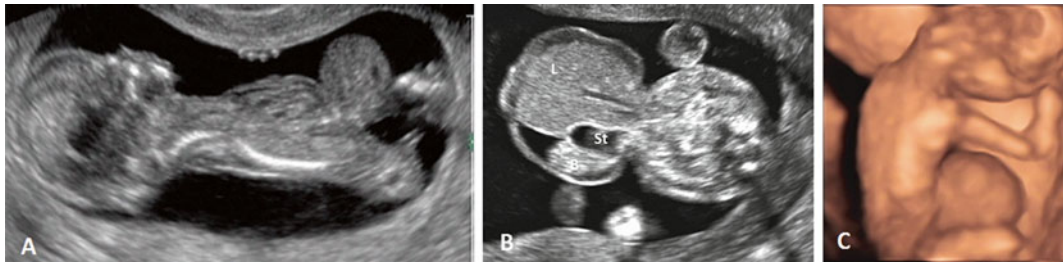

Fig. 19.18 Fetus with a liver-containing omphalocele at 12 weeks. (**a**) Sagittal view of the fetus showing the liver-containing omphalocele. (**b**) Transvaginal transverse section of the omphalocele sac reveals the liver (L), bowel (B), and the stomach (St) within the sac. (**c**) 3D reconstruction of the liver-containing omphalocele. Note that in comparison to the gastroschisis, this defect is enveloped in a peritoneal sac and the outer surface is smooth

liver-containing omphalocele was 1:3360 [19]. Fifty-five percent of the bowel-containing omphaloceles had a chromosomal abnormality, with trisomy 18 (56.8 %) being the most common, followed by trisomy 13 (25.7 %), monosomy x (45 XO or Turner syndrome) (8.1 %), and trisomy 21 (4.1 %). Of the liver-containing omphaloceles, 52.9 % had a chromosomal abnormality of which trisomy 18 accounted for 66.7 % and trisomy 13 for 33.3 %. In these cases, though normal nuchal translucency (NT) presents a risk of aneuploidy of 28 %, as the NT measurement increases, there is a direct correlation with a steady increasing likelihood of aneuploidy [19, 55, 56]. Omphalocele is also associated with other malformations and syndromes including Beckwith-Wiedemann syndrome, neural tube defects and diaphragmatic defects. Postnatal complications are related not only to aneuploidy type but also to size of the defect and extent of liver herniation [57].

Limb-body wall complex, *OEIS syndrome*, and *Pentalogy of Cantrell* are rare major abdominal wall defects. Limb-body wall complex is a uncommon defect in which at least three of the following defects are present: exencephaly/encephalocele with facial clefts; thoraco-abdominoschisis/ventral body wall defect and limb defects [58]. Russo et al. [59] has proposed that there are two clearly distinguishable phenotypes: "placento-cranial" and "placento-abdominal." The "placento-cranial defects" are characterized by encephalocele or exencephaly always associated with facial clefts and amniotic band between the cranial defects and placenta. The second phenotype, the "placento-abdominal defects," has urogenital anomalies, anal atresia, lumbosacral meningocele, and placental anomalies such as presence of short cord, persistence of extraembryonic coelom, and intact amnion (Fig. 19.19).

OEIS syndrome is a rare condition with a prevalence of 1: 200,000–1:400,000 pregnancies. The pathogenesis remains largely unknown [60]. The typical findings are omphalocele, exstrophy of cloaca, imperforate anus and spinal defect; other malformations such as renal, single umbilical artery and limb defects are commonly seen with OEIS [61].

Bladder exstrophy can be identified in the first trimester as a large, lower abdominal wall cystic mass, lack of visualization of an intra-abdominal bladder, low umbilical cord insertion as well as the presence of umbilical cord cysts [62] (Fig. 19.20). Later in the second trimester the large cystic lower abdominal mass disappears, as the exstrophied bladder ruptures and results in a hyperechoic lower abdominal wall bulge, with lack of visualization of an intra-abdominal bladder. The umbilical cord cysts may or may not be seen as the pregnancy progresses. Additional features include an abnormally small phallus with anteriorly displaced scrotum [63]. Bladder exstrophy is more common in males than in females and, in addition to the bladder defect, there is also an abdominal wall, pelvic floor, and bony pelvis defect. Sensitivity of early detection is low without associated findings and potential mimicking of bladder presence through presence

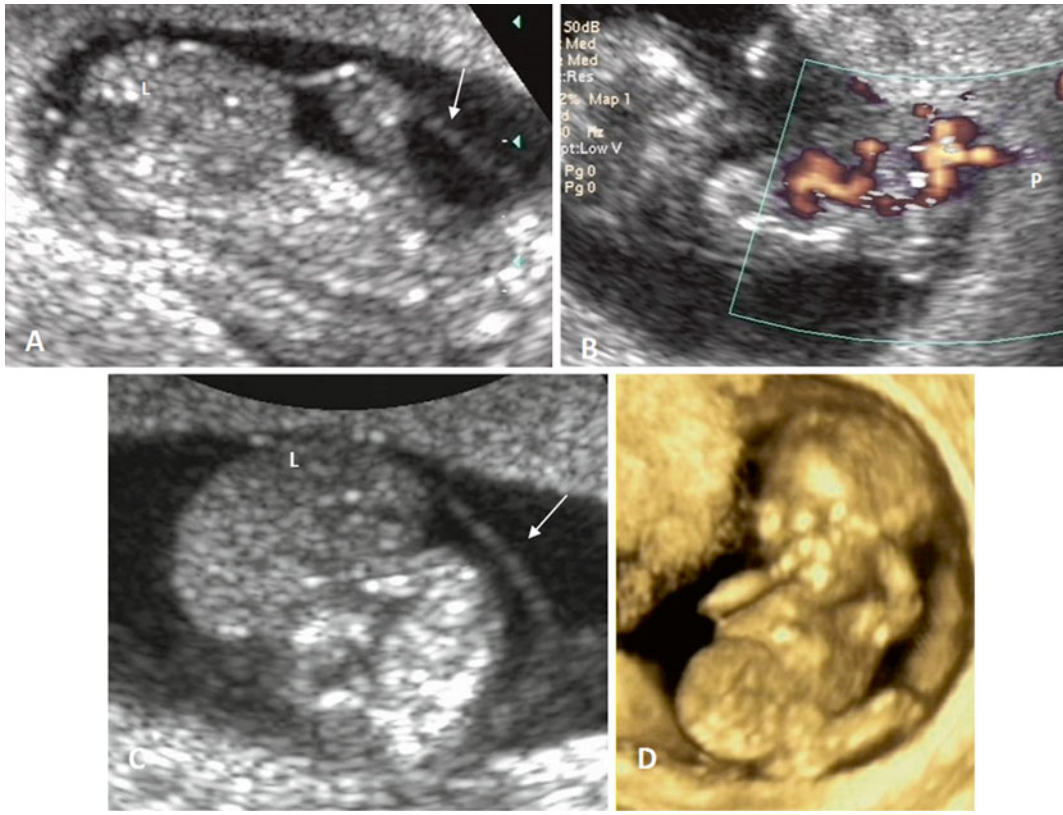

Fig. 19.19 Fetus at 11 1/7 weeks with the limb-body wall complex; sonography most consistent with placenta-abdominal type. (**a**) The amnion (*arrow*) is seen closely surrounding the fetus consistent with oligohydramnios; the liver (L) is seen extracorporeally with no distinct membrane covering. (**b**) The fetus is essentially attached to the placenta (P) by the very short umbilical cord. Power Doppler demonstrates the short cord. (**c**) Transverse section at the level of the abdominal wall defect reveals the extracorporeal liver (L) and the amnion, which is closely applied to the fetal body (*arrow*). (**d**) 3D reconstruction depicting the abdominal wall defect and of the lower extremity deformity

of a urachal cyst [54, 64, 65]. It can be associated with the aforementioned OEIS complex or cloacal malformation. Various associated anomalies include renal, neural tube defects, omphalocele, hydrocolpos, umbilical cord cysts, and separated pubic bones [64, 66].

Pentalogy of Cantrell is another rare condition with prevalence ranging from 1:65,000 to 200,000 with five anomalies that encompass this malformation: (1) a median supraumbilical abdominal wall defect; (2) a defect of the lower sternum; (3) a deficiency of the anterior diaphragm; (4) a defect of the diaphragmatic pericardium; and (5) intracardiac defects [67]. This sequence may result in ectopia cordis as well as an omphalocele but other intra-abdominal structures may also be seen as extra-corporal (Fig. 19.21). This condition has been associated with the common trisomies (21, 18, and 13).

Extremities

Hand Malformations, Polydactyly, Sirenomelia

In the first trimester it is possible to accurately identify and measure the three components of the extremities. In the upper limbs these are: arms (humerus), forearms (ulna, radius), and hands; in the lower extremities the thighs (femur), legs (tibia, fibula), and feet. Their detection rate is in greater than 95 % of the cases [68, 69].

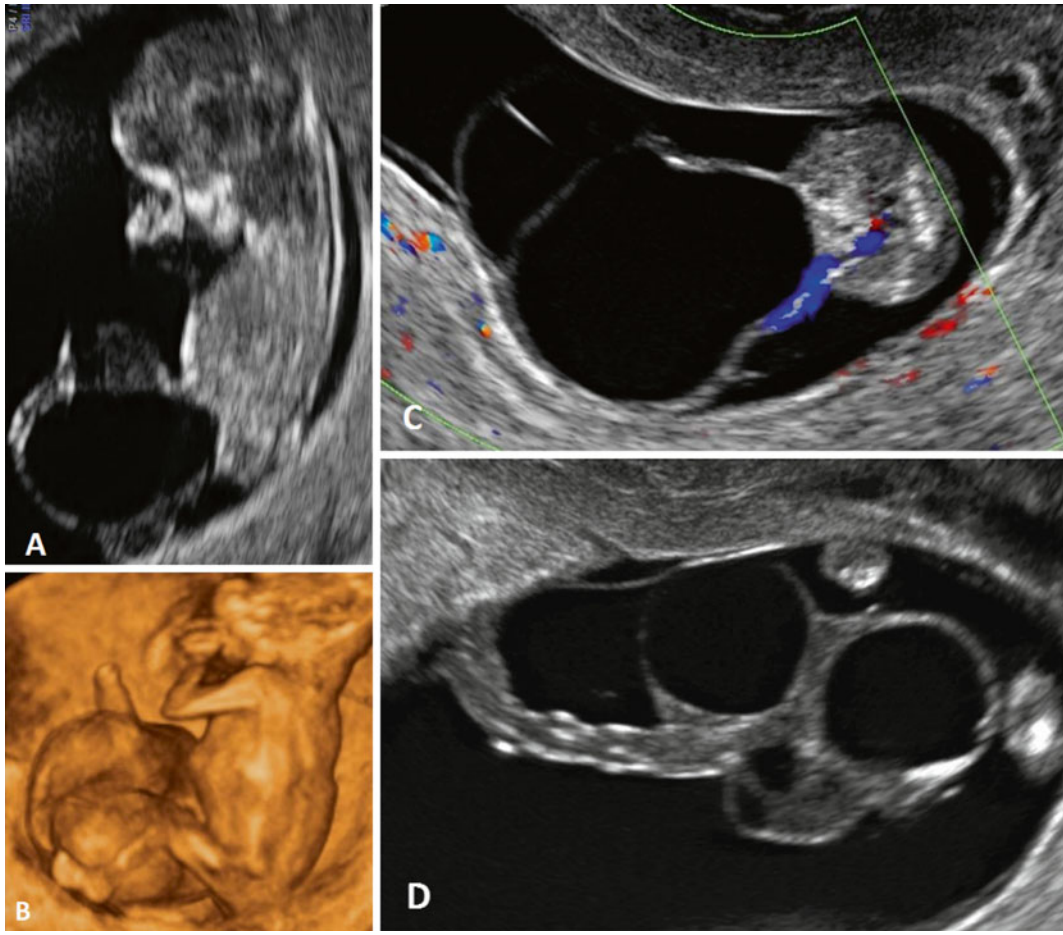

Fig. 19.20 Fetus at 11 5/7 weeks with exstrophy of the bladder and umbilical cord cysts. (**a**) Sagittal view of the fetus shows a large cystic lower abdominal wall mass, the fetal bladder at the same time; no fetal bladder was identified within the pelvis. (**b**) 3D reconstruction of exstrophy of the bladder. (**c**) Transverse section at the level of the exstrophied and dilated bladder is seen; using color Doppler a single umbilical cord was seen. (**d**) The umbilical cord reveals two cord cysts; cord cysts are often seen with exstrophy of the bladder

Our group reported detection rates of over 97 % for the upper extremity and over 95 % for the lower extremities [7] (Fig. 19.22). Detection rate of limb anomalies may be low, if they are isolated findings. Gray et al. [70] enrolled 100 patients with congenital upper extremity reduction or duplication anomalies and reviewed their prenatal records. Prenatal diagnosis was made in 31 % of the cases. In a recent study, Bromley et al. [1] reported a 38.8 % detection rate of anomalies involving the extremities at ≤14 weeks, although they did not have a defined imaging protocol.

Limb anomalies have a prevalence of approximately 6/10,000 live births; with a higher occurrence of anomalies occurring in the upper limbs. Unilateral limb anomalies are more common than bilateral and the right side is more likely to be affected than the left side [71]. In a study looking at forearm anomalies 9 of the 66 were diagnosed between 11 and 13 6/7 week; 29.7 % had a chromosomal aneuploidy of which trisomy 18 was the most common abnormality; 29.7 % had genetic syndromes such as Cornelia de Lange and VATER syndrome; the anomalies were isolated in 23 % [72] (Fig. 19.23).

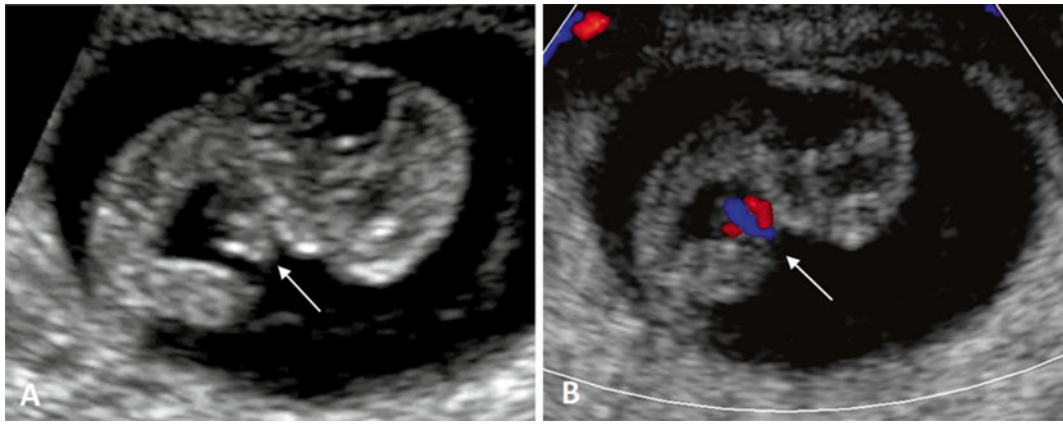

Fig. 19.21 Fetus at 9 1/7 weeks with ectopia cordis and omphalocele. (**a**) Sagittal view of the fetus showing the heart pulsating outside the fetal thorax as well as a liver-containing omphalocele. (**b**) Using color Doppler the fetal heart is seen to be protruding through the chest. Given the other anomalies this fetus likely had Pentalogy of Cantrell; fetal karyotype revealed trisomy 16. Courtesy of Patricia Mayberry, RDMS

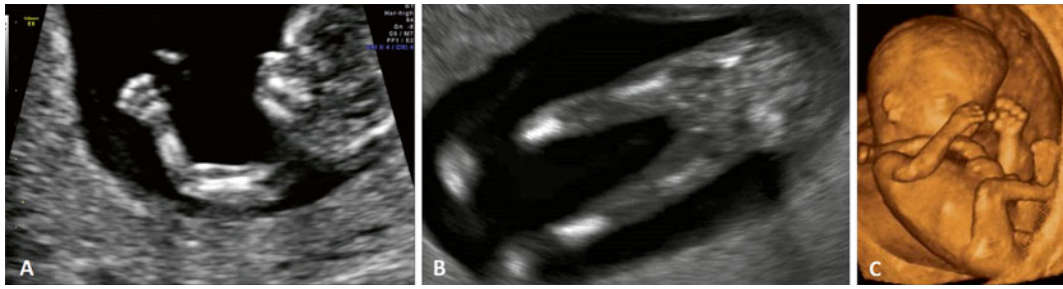

Fig. 19.22 Fetus at 12 5/7 weeks. (**a**) The normal upper extremity is seen demonstrating the three components of the limb the humerus, radius/ulna, and hand. (**b**) The two lower extremities are seen. (**c**) 3D reconstruction of the fetus showing the normal upper and lower extremities

Sirenomelia (mermaid syndrome) is a rare and fatal condition of uncertain etiology; the condition is characterized by fusion of the lower extremities resulting in a single limb. Other anomalies seen are urogenital, gastrointestinal and single umbilical cord (Fig. 19.24) [73].

The Placenta

Subchorionic Hematoma, Placental Attachment Disorders

In the first trimester, subchorionic hematomas may be seen as crescent shaped anechoic or hypoechoic regions at the placento-decidual interface. This disruption may occur due to inherent placental dysfunction with controversial, but likely somewhat increased risks of placental abruption and preterm premature rupture of membranes. Subchorionic hematomas are relatively common findings during the first-trimester scan with reported incidence of 0.5–22 % [74]. When the size of the hematoma measures greater than 25 % of the gestational sac size, there was a twofold increased risk of pregnancy loss [74]. In addition, retroplacental hematomas render a higher risk to pregnancy outcome than do marginal bleeds [75] (Fig. 19.25).

It is critical to evaluate the implantation site in order to identify morbidly adherent placentas or cesarean scar pregnancies. Please refer to Chap. 17 for further discussion.

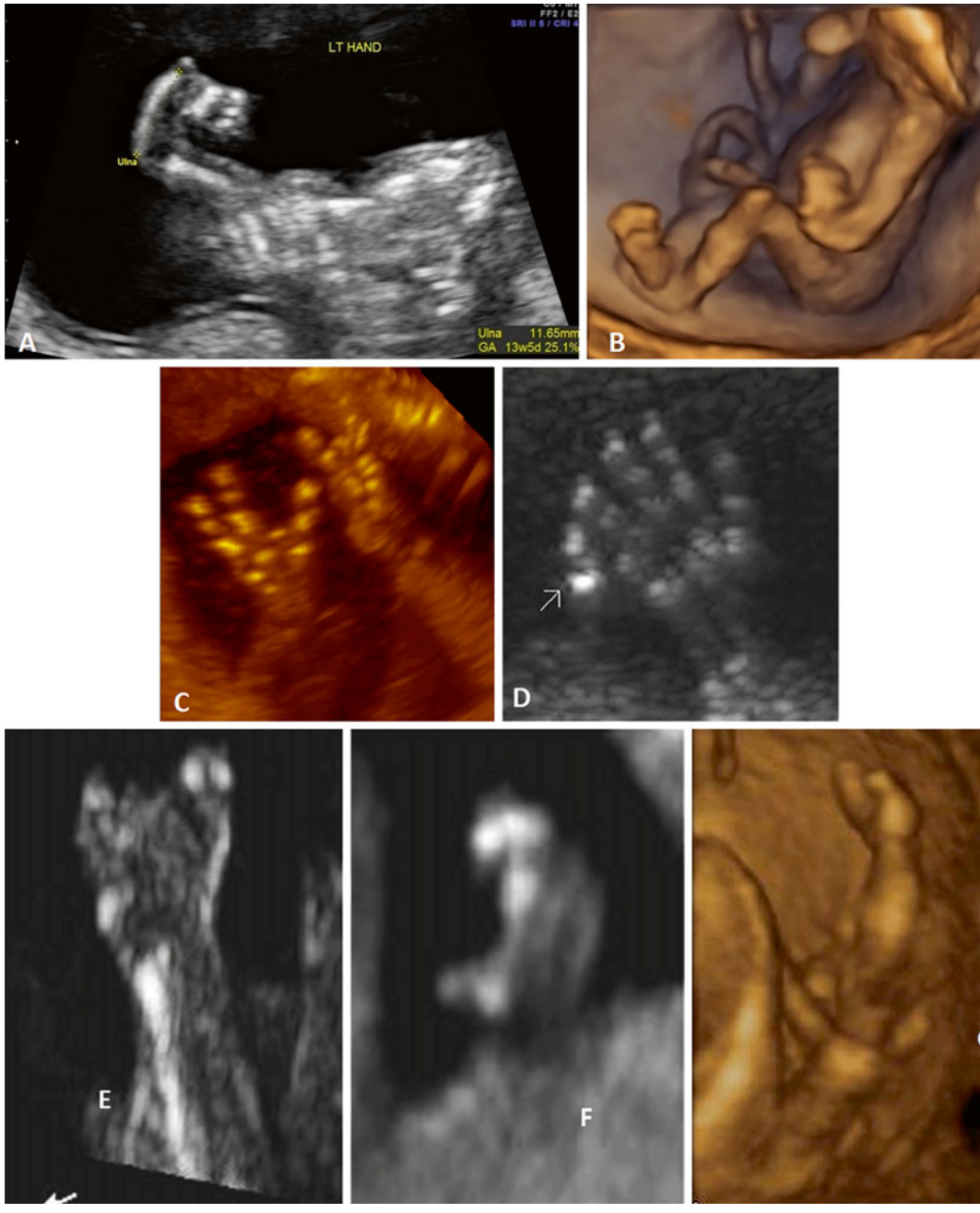

Fig. 19.23 A composite image of several fetuses with different upper extremity abnormalities. (**a**) Fetus at 13 5/7 weeks demonstrating bilateral clubbing of the hands, fetal karyotype was consistent with trisomy 18. (**b**) 3D reconstruction of the clubbed hands of the fetus with trisomy 18. (**c**) Fetus at 14 weeks with ectrodactyly (*split hand*). (**d**) Fetus at 14 weeks with post-axial polydactyly. (**e**–**g**) Multiple views of a fetus at 11 weeks with ectrodactyly

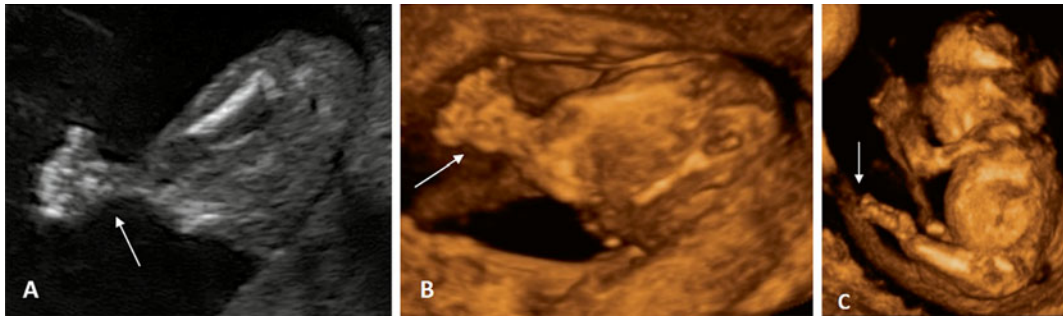

Fig. 19.24 Fetus at 12 weeks with sirenomelia. (**a**, **b**) are targeted views of the single fused lower extremities. (**c**) 3D reconstruction of the sirenomelia

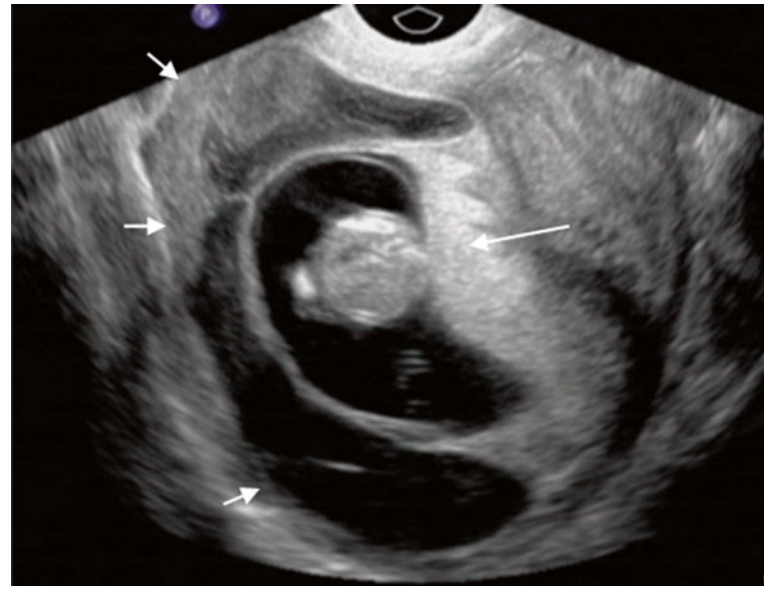

Fig. 19.25 Subchorionic hematoma in a fetus at 13 weeks; the *smaller arrow* point to the hematoma which is large but does not involve the placenta (*large arrow*)

Umbilical Cord

Two-Vessel Cord

The normal umbilical cord contains one vein and two arteries and can be identified in the first trimester. The two arteries can be identified by color or power Doppler mode by indirect inference, imaging the vessels bilaterally bordering the fetal bladder wall on the pelvic cross-section. Due to ease and speed of obtaining this image, the ALARA principle is not compromised. A two-vessel cord implies the presence of a single umbilical artery (SUA). This anomaly is one of the most common ultrasonographic findings in pregnancy; it is seen in 0.5 % to upwards of 6 % of singleton gestations with a sensitivity quoted between 57.1 and 84.2 and specificity of 98.9–99.8 in the first trimester [76–78]. Incidence increases three to four times in twin gestations [78, 79]. SUA is associated with congenital malformations and chromosomal aneuploidies in 10 % of cases [80], but also preterm birth, growth restriction, and poor fetal outcomes [78]. Congenital malformations are identified during first trimester scans in 17 % of cases, with an additional 7 % found during the second trimester [77]. The majority of malformations

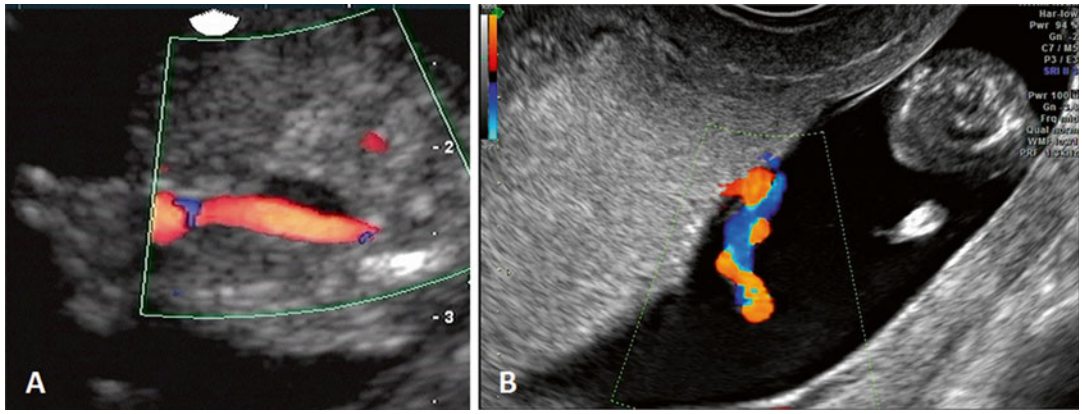

Fig. 19.26 First-trimester single umbilical artery. (**a**) Using color Doppler only a single artery is seen flanking the fetal bladder in a fetus at 11 6/7 weeks. (**b**) The umbilical cord insertion into the placenta is seen in a 11 5/7 weeks pregnancy with the single umbilical artery

associated with SUA is genitourinary or cardiac in nature, but may also include congenital diaphragmatic hernias, musculoskeletal anomalies, exstrophy of cloaca sequence, sirenomelia, or VATER syndrome [81–83] (Fig. 19.26).

Summary

In 2014 a consensus statement on fetal imaging was published [84]. This statement went on to say that "Offering first-trimester screening for aneuploidy assessment at 11 to 13 6/7 weeks of gestation is recommended by the American College of Obstetricians and Gynecologists. If a late first trimester ultrasonography is performed for dating or nuchal translucency assessment, evaluation for early detection of severe fetal anomalies such as anencephaly and limb-body wall complex is reasonable. In some experienced centers, detection of other major fetal anomalies in the first trimester is possible" [84]. This statement brought to the forefront the fact that fetal anomalies can be detected in the first trimester. The goal of this chapter was to further raise awareness and to promote the reality that first trimester anatomy scan and detection of fetal anomalies at the time of the "nuchal scan" is feasible and should be strongly considered even in the era of increasing use of noninvasive prenatal diagnosis. Also it is important to realize that a significant number of fetal anomalies can be diagnosed reliably. The most important information is that diagnosis of lethal and major anomalies have very high detection rates and, in some studies, this number is as high as 100 % for anomalies such as exencephaly–anencephaly sequence, cephalocele, holoprosencephaly, and megacystis. During the "nuchal scan" it is important not only to correctly measure the NT and assess the nasal bone, but to look at the rest of the fetus. "*Search for fetal anomalies and you shall find them*."

Teaching Points

- The detection of fetal anomalies in the first trimester is possible.
- When anomalies are looked for in a systematic fashion detection rates are as high as 80 %.
- Transabdominal and transvaginal sonography in combination increase detection of fetal anomalies in the first trimester.
- Exencephaly–anencephaly sequence, omphalocele, gastroschisis, and holoprosencephaly are anomalies with 100 % detection rates reported in the first trimester.

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Invasive Procedures in the First Trimester

20

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Introduction

Nearly 20 years ago we published a paper entitled: "Integration of Genetics and Ultrasound in Prenatal Diagnosis: Just looking is not enough" [1]. Our thesis was, and it remains just as true today, that ultrasound visualization is an important part of prenatal diagnosis, but basically only represents half the story. In this 1996 study we found that 42 % of fetal genetic and congenital abnormalities were not detectable by ultrasound. Thus, in this very comprehensive volume on first-trimester ultrasound, this chapter is the one dealing with the issue: "Oh, by the way, ultrasound can't do everything." Similarly, societies such as the International Society for Ultrasound in Obstetrics and Gynecology (ISUOG) not surprisingly, focus on ultrasound and can sometimes lose the perspective that, in fact, it is just part of the evaluation. The opposite is true for the American College of Medical Genetics and the International Society for Prenatal Diagnosis, in which the role of ultrasound in prenatal diagnosis is sometimes underplayed.

The reality is that competence in both areas is essential for optimal fetal evaluation. Prenatal diagnosis and reproductive choice are issues that go far beyond medicine, per se. As the political fights over women's reproductive rights are likely to heat up even further in the coming years, with possible further restrictions on how far into pregnancy a woman can terminate a pregnancy, early accurate first-trimester diagnosis will become even more necessary.

As has been detailed extensively in the previous chapters in this volume, the use of ultrasound has become an essential part of the modern management of every pregnancy. Concomitant with the development of ultrasound for prenatal diagnosis in the early 1970s, also came the beginnings of directly obtaining fetal tissue (amniotic fluid cells) in the late 1960s and 1970s. Without ultrasound guidance, most amniocenteses were performed at 17+ weeks, to minimize the chance that the blindly inserted needle would hit something important, but accidental damage did occasionally occur [2].

Improvements in ultrasound led to better visualization which, in fact, created the concept of parental bonding from viewing the fetal form on ultrasound [3]. There is also a psychological

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transition from a state of "I am pregnant" to "I am going to have a baby." These are very different emotional states and helped drive the desire to move prenatal diagnosis and screening from the second trimester to the first. Aneuploidy screening is covered in Chap. 8, so we will concentrate here on diagnostic and therapeutic interventions.

In the late 1980s we predicted that most diagnostic procedures would move into the first trimester in the 1990s [4]. That was proceeding on schedule at the most sophisticated centers, until the limb reduction defect scare was used to turn patients away from chorionic villus sampling (CVS), and to promote amniocentesis which could be done by a much larger number of physicians who, therefore, did not need to refer patients to CVS centers. Now that first-trimester screening is becoming the norm, we expect that most diagnostic procedures will finally be done in the first trimester.

Chorionic Villus Sampling

More than three decades of experience have shown that CVS, in experienced hands, is both safe and effective [5, 6], despite allegations in the early 1990s of increased risk of birth defects [7, 8], which have been clearly disproven by objective data (although still disputed by some). CVS gained rapid acceptance, then decline, and now reacceptance in prenatal diagnosis, in the hands of experienced operators.

In the 1980s several US and European centers began performing CVS for the purpose of prenatal diagnosis in the clinical setting. Multiple single institution and collaborative papers documented its accuracy and safety [9, 10]. Following the 1990 FDA approval of the Trophocan™ catheter (Concord/Portex; Keene, NH) for use in transcervical (TC) CVS, an increasing number of US physicians began offering the procedure. After the limb reduction defect (LRD) scare in the early 1990s, Portex withdrew their catheter [7, 8]. Today, the vast majority of TC procedures are performed using the "Cook" catheter.

In some states, there were requirements to perform numerous procedures on non-continuing pregnancies to gain experience prior to clinical use. Others had no guidelines or regulations. This led to wide and haphazard introduction and was a predicate to the Fetal Medicine Foundation's attempt to guide the introduction of nuchal translucency screening to improve quality control [11].

Indications

The most common indications for CVS are advanced maternal age, abnormal screening results for aneuploidy, or molecularly diagnosable genetic disorder. The recent advances in higher definition molecular karyotyping using array comparative genomic hybridization (aCGH), also known as microarrays (MCA), have shown that in patients with an ultrasound abnormality, the detection of pathologic copy number variants (CNVs) with duplications or deletions smaller than visible by traditional cytogenetic techniques, is approximately 6–8 % [12, 13]. In pediatrics, for example, developments of aCGH have, over the past decade, gained rapid acceptance and market share in pediatrics. The cytogenetic evaluation of dysmorphic children is now routinely done with aCGH rather than karyotype, because the yield is about twice as high [13].

In prenatal patients with no abnormalities by history, ultrasound, or karyotype, the minimal yield of clearly pathological CNVs is at least 1/200 for all pregnancies [12, 13]. Counting those CNVs that are felt likely to be pathological, although the database is not yet complete enough to be certain, that number is likely well over 1 % and possibly 1.7 %. As such, all women have a risk higher than the 0.5 % attributable to a 35-year-old, which has been the standard to offer diagnostic procedures for the last four decades.

With the sometimes exception of those patients whose primary risk is for a neural tube defect, any patient considered a candidate for amniocentesis could be offered CVS, if they are seen in the first trimester. CVS has the advantage of earlier diagnosis, allowing earlier intervention when chosen by the patient, and usually ensuring privacy in reproductive choices.

Multiple Gestations

We routinely perform CVS on multiple pregnancies [14, 15]. It is considerably more difficult to do than on singletons because precise visualization of the needle or catheter is required because the pathway for aspiration needs to avoid the other placentas. In very experienced hands it is extremely accurate, however, although there is always a small percentage risk for cross contamination with adjacent placentas [14, 15]. In our experience such cross contamination has not been a clinical problem. With 3 % of all gestations in the USA now being multiples and given that the infertility population on average is older than the average, a disproportionate number of multiple pregnancy patients are likely to want diagnostic procedures [15]. We routinely perform CVS, run FISH analysis for chromosomes 13, 18, 21, X, and Y overnight, and then perform fetal reductions (FR) the next day [14]. We have found this approach to be highly accurate, and it allows the couple to combine CVS and FR in one visit, rather than having to return 2 weeks later [15, 16]. Our usual approach for multiples considering FR is to test one more fetus than the parents are intending to keep. This virtually assures that there will be at least the intended number that are normal, and can then give them a gender preference option in selected situations (described in detail later in this chapter) [17]. In the setting of a "vanishing twin," which may occur in up to 3 % of pregnancies [18], studies suggest an increased risk of aneuploidy in the remaining placental tissue of the "vanished twin" [19]. Therefore, care must be taken during sampling if only the remaining twin is being evaluated.

Procedure

We believe genetic counseling is very important particularly since, in the past few years, there has been considerable complexity added to patient's decisions with new technologies, such as cell free DNA and enhanced molecular screening and diagnostic tests, now available.

We also counsel our patients that, for most of them (without significant history or ultrasound anomaly) in the middle 99 %, it does not matter whether they have any procedure or not. The issue really is that "if they are going to be wrong, which way would they rather be wrong?" Would they rather take a small risk of having a baby with a significant problem or on the other extreme a small risk of having a complication because they wanted to know that? Patients have to also consider the implications of either extreme and decide "what do they fear the most," and we can minimize that at the expense of the other.

The next step is the ultrasound evaluation. First, fetal viability is confirmed. About 2 % of patients are discovered to have a blighted ovum or an embryonic/fetal demise. This percentage was much higher 20 years ago when ultrasounds in the first trimester were less common [20]. Fetal size discrepancies should also be noted. The smaller-than-expected fetus, even in the first trimester, is at increased risk for aneuploidy [21, 22]. Such cases merit CVS for earlier diagnosis.

Placental evaluation is of utmost importance in properly assessing patients for CVS as it determines whether the approach will be transcervical (TC) or transabdominal (TA). If the placenta is low-lying and posterior, a TC approach is appropriate. Such cases may be attempted by novices under supervision. If the placenta is anterior and fundal, an abdominal approach is usually indicated. The placenta can often be maneuvered towards a vertical or horizontal configuration by judicious manipulation of bladder volume to make the desired approach easier (Fig. 20.1).

In our own experience, we perform the TC approach in about 70 % of singletons. Less experienced operators have a much higher proportion of TA cases because TA is usually easier for the inexperienced physician, as it is very comparable to doing an amniocentesis. The TC approach is more difficult and requires more experience to be competent and safe. Both approaches require a three-dimensional (3D) appreciation of the anatomy to be interpreted from 2D ultrasound. We have found that there is a divide that cannot be overcome just by experience between those physicians and sonographers who are capable of thinking and acting in 3D and those who cannot.

We have also seen operators who do not perform TC procedures have use contortions of

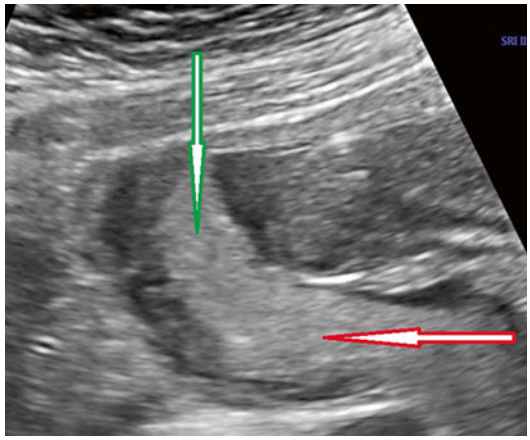

Fig. 20.1 Approaches to CVS: transcervical (*red horizontal arrow*) and transabdominal (*green vertical arrow*)

lifting the uterus vaginally to make it reachable abdominally. We think this is inappropriate and increases the risk of procedures when they are done by the wrong approach for the given location. We believe that a CVS operator must be proficient in both approaches.

Other factors must be considered before attempting CVS. At times the patient gives a history of genital herpes simplex or a recent group B streptococcus (GBS) infection. Such cases should be individualized, and the small or theoretical risk of introducing an infection into the fetal-placental tissues should be discussed with the patient. TA-CVS or amniocentesis are usually offered when a significant risk of active GBS is present, as data are in favor that uterine infection, in such cases, might occur almost entirely after TC aspiration [21]. The choice of whether to perform TA-CVS or TC-CVS should be made according to the experienced operator's judgment, based on the previously described conditions and in accordance with the patient's bacterial/fungal cervical carrier status when known [14].

Safety

Over the past three decades, multiple reports from individual centers have demonstrated the safety and low rates of pregnancy loss following CVS [22, 23]. There is a large amount of literature, which will not be extensively reviewed here, from the 1980s and 1990s that has detailed the development of CVS as a clinical procedure and led to the US Food and Drug Administration's removal of the restrictions on the use of the CVS catheter in 1989. The large majority of these projects did not find any increased risk of CVS over amniocentesis, but overall loss rates of both procedures were considerably higher than claimed by many operators of both procedures [22, 23].

Table 20.1 Amniocentesis and CVS loss rates[a]

Loss before	Amniocentesis (%)	CVS (%)
14 days	0.6	0.7
24 weeks gestation	0.9	1.0
Total	1.9	2.0

[a]Created with data from ref. [5]

Three studies in the past decade have been very important in our current understanding. The first was a meta-analysis published in 2007 by Mujezinovic and Alfirevic [5]. Because of the higher background rate of loss in the first trimester, CVS would be expected to have a higher overall loss rate. Yet it is impossible precisely to parse which losses are procedure-related, as opposed to background. What they reported is that, in experienced centers, the loss rates within 2 weeks of the procedure, up to 24 weeks and at term were essentially identical (Table 20.1).

The second study is the recent ongoing experience of the Danish first-trimester screening program, which over the past several years has maintained a very high detection rate for Down syndrome (>90 %) while cutting their false positive rates in half. As a consequence of first-trimester screening, the utilization of CVS in Denmark has been three times that of amniocentesis. Their data show that the procedure risk of CVS is as low (and possibly lower) than amniocentesis [24]. Furthermore, the incidence of late complications such as late demise was significantly lower in CVS patients than amniocentesis patients.

Recently Akolekar published a meta-analysis that demonstrated that overall procedure loss rates for CVS and amniocentesis were much lower than previously shown, and not different

from each other—approximately 1/500 [6]. The primary confusion is the difference in background loss rates, which actually explain the vast majority of any differences between the two procedures.

Overall, we counsel our patients as to a 1/400 procedural risk of either CVS or amniocentesis in very experienced hands. These risks may, in fact, err on the side of being too high in our hands, but we do not want patients taking these decisions frivolously without considering the possibility of loss. Importantly, both procedures have considerably higher risks in inexperienced physicians or those who cannot visualize the anatomy in a 3D manner as described above. As such we believe that both CVS and amniocentesis should be performed preferably in "centers of excellence" by physicians, with experienced sonographers, who perform the procedure regularly—and not as an occasional item.

Complications of Chorionic Villus Sampling

Bleeding

Vaginal bleeding is seen in as many as 7–10 % of patients sampled TC but is less common after TA-CVS. Minimal spotting is more common and may occur in almost one-third of women sampled by the TC route [9, 25]. In most cases, the bleeding is self-limited, and the pregnancy outcome is excellent.

Infection

Since the initial development of TC-CVS, there has been concern that TC-CVS would introduce vaginal flora into the uterus. This possibility was confirmed by cultures that isolated bacteria from up to 30 % of catheters used for CVS [26, 27]. In clinical practice, however, the incidence of post-CVS chorioamnionitis is low [9, 10]. Infection following TA-CVS also occurs and has been demonstrated, at least in some cases, to be secondary to bowel flora introduced by inadvertent puncture by the sampling needle.

Rupture of Membranes

Gross rupture of the membranes days to weeks after the procedure is acknowledged as a possible post-CVS complication. Rupture can result from either mechanical or chemical injury to the chorion, allowing exposure of the amnion to subsequent damage or infection. One group reported a 0.3 % incidence of delayed rupture of the membranes following CVS [28], a rate confirmed by Brambati et al. [29]. Unexplained, mid-trimester oligohydramnios has also been suggested as being a rare complication of TC-CVS.

Risk of Fetal Abnormalities Following Chorionic Villus Sampling

In the early 1990s it was suggested that CVS may be associated with specific fetal malformations, particularly limb reduction defects (LRDs). Today, based on the published data, it appears safe to state that there is no increased risk for LRDs, or any other birth defect, when CVS is performed at >70 days of gestation [30–33].

The first suggestion of an increased risk for fetal abnormalities following CVS was reported by Firth et al. [7]. In a series of 539 CVS-exposed pregnancies, there were five infants with severe limb abnormalities in a cohort of 289 pregnancies sampled by TA-CVS at 55–66 days gestation. Four of these infants had the unusual and very rare oromandibular-limb hypogenesis (OLH) syndrome, and the fifth had a terminal transverse LRD. OLH syndrome occurs in 1 per 175,000 live births [34], and LRDs normally occur in 1 per 1690 births [35]. Thus, the occurrence of these abnormalities in more than 1 % of CVS-sampled cases raised a high level of suspicion. Subsequently, other groups reported the occurrence of LRDs and OLH following "early" CVS [36–41]. In 1992, a case–control study using the Italian Multi-Center Birth Defects Registry, reported an odds ratio of 11.3 (95 % CI 5.6–21.3) for transverse limb abnormalities following first-trimester CVS [36]. However, when stratified by gestational age at sampling, pregnancies sampled prior to 70 days had a 19.7 % increased risk of

transverse limb reduction defects, while patients sampled later did not demonstrate significantly increased risk. Other case–control studies, however, have not seen any association of CVS with LRDs [31, 32].

The risk for fetal malformations is real when CVS is done at an earlier gestation age, i.e., during the period of limb genesis at 6–7 weeks [7, 8, 38]. Brambati et al., practicing in Milan, have a large population at risk for β thalassemia. The population is also predominantly Catholic, for whom abortion at any gestational age is religiously proscribed. However, to assuage the guilt of wanting diagnosis, they wanted it done as early as technically possible. They reported a 1.6 % incidence of severe LRDs in a group of patients sampled at 6 and 7 weeks gestation [38]. This rate decreased to 0.1 % at 8–9 weeks. These data support the assumption that early gestational sampling and excessive placental trauma may be etiologic in the reported clusters of post-CVS LRDs.

In the USA, the population group most interested in early CVS has been the Orthodox Jewish community—at high risk for Tay Sachs and other Ashkenazi diseases. In the observant Jewish community, abortion is permitted, by religion, until 40 days post-conception (7 weeks 5 days from LMP). Wapner and Evans have shown that, in very experienced centers, CVS can be safely and reliably performed, even in very early gestation [30]. In a study they conducted, CVS was performed at less than 8 weeks gestation in a population of Orthodox Jews. Of the 82 cases of early CVS, there was only a single case of severe LRDs, a rate of 1.6 %. While this risk is considerably higher than when done at the usual time, we believe that in comparison to a 25 % risk of lethal disorder and with proper genetic counseling, it could be a reasonable decision for a couple to make. However, in the one case, despite the patient having had three previous early CVSs, they chose to sue the doctor stating that they did not "know." As a result of the legal exposure, virtually all centers that were willing to do the procedure, stopped performing it.

The question whether CVS sampling after 10 weeks has the potential of causing more subtle defects, such as shortening of the distal phalanx or nail hypoplasia, was a major concern, debated thoroughly in the literature [40, 42]. The overall incidence of LRDs after CVS is estimated to be 1 in 1881 (ranging from 5.2 to 5.7 per 10,000), compared with 1 in 1642 (ranging from 4.8 to 5.97 per 10,000) in the general population [33, 42]; hence, there are no data to substantiate this concern. As noted, in most experienced centers performing CVS after 10 weeks, no increase in limb defects of any type was observed [31, 33, 41, 42].

Perinatal Complications

No increases in preterm labor, premature rupture of the membranes, small-for-gestational age infants, maternal morbidity, or other obstetric complications have occurred in sampled patients [43]. Although the Canadian Collaborative Study showed an increased prenatal mortality in CVS sampled patients, with the greatest imbalance being beyond 28 weeks, no obvious recurrent event was identified [10]. To date, CVS is not considered to harbor additional prenatal complication as long as the procedure is performed by an experienced operator and after 10 weeks gestation.

Long-Term Infant Development

Long-term infant follow-up has been performed by Chinese investigators who evaluated 53 children from their initial placental biopsy experience of the 1970s. All were reported in good health, with normal development and school performance [44]. Schaap et al. [45] obtained long-term follow-up data after CVS and amniocentesis and found no significant differences for neonatal and pediatric morbidity. Based on their data, the authors concluded that TC-CVS performed around 10 weeks gestation is not associated with an increased frequency of congenital malformations, compared with second trimester amniocentesis.

Accuracy of CVS Cytogenetic Results

A major concern with all prenatal diagnostic procedures is the possibility of discordance between the prenatal cytogenetic diagnosis and the actual fetal karyotype. With CVS, these discrepancies can occur from either maternal tissue contamination or from true biologic differences between the extraembryonic tissue (i.e., placenta) and the fetus. Fortunately, genetic evaluation of chorionic villi provides a high degree of success and accuracy, particularly in regard to the diagnosis of common trisomies [46]. In the late 1980s, the US Collaborative Study revealed a 99.7 % rate of successful cytogenetic diagnosis, with 1.1 % of the patients requiring a second diagnostic test, such as amniocentesis or fetal blood analysis, to further interpret the results [46]. In our own experience, a follow-up amniocentesis is needed about 0.5 % of the time.

Clinical errors or misinterpretation are rare, however, and the need for repeat testing continues to decrease, as more knowledge about the characteristics of chorionic villi is obtained. Indeed, studies [23, 47] have demonstrated that CVS is associated with a low rate of maternal cell contamination or chromosomal abnormalities confined to the placenta, as will be described below. For example, tetraploidy on CVS FISH and culture is seen in about 0.5 % of cases and is known to almost always be associated with a normal diploid fetus.

Maternal Cell Contamination (MMC)

Contamination of samples with a significant amount of maternal decidual tissue may lead to diagnostic errors, underlining the importance of preventing this occurrence [27, 47]. Generally, decidual contamination in CVS is almost always due to a small sample size, making appropriate tissue selection difficult. In experienced centers, in which adequate quantities of tissue are available, this problem is rare, with clinically significant MCC occurring in less than 0.5 % of CVS procedures. It is standard to separate maternal tissue from the sample. The chorionic "fronds" are distinguished from the maternal decidua under the microscope, making decidual removal by careful dissection possible.

In recent years there has been much progress in the molecular techniques suitable for detection of MMC, allowing more accurate results in cases of molecular diagnoses, where MMC may jeopardize the validity of the test.

Confined Placental Mosaicism

True discrepancies between the karyotype of the villus and the actual fetal karyotype can occur, leading to either false-positive or false-negative clinical results. Although initially there was concern that this might invalidate CVS as a prenatal diagnostic tool, subsequent investigations have led not only to a clearer understanding of the clinical interpretation of villus tissue results, but also revealed new information about the etiology of pregnancy loss, possible causes of intrauterine growth restriction (IUGR), and the biologic mechanisms for uniparental disomy and associated clinical syndromes.

A chromosomal aberration that does not involve the fetal cell lineage will produce a confined placental mosaicism (CPM), in which the trophoblast and perhaps the extraembryonic mesoderm may demonstrate aneuploid cells, but the fetus is euploid. Several mechanisms may apply in pregnancies where CVS mosaicism or non-mosaic feto-placental discrepancies are detected.

Mosaicism occurs in about 0.5 % of all CVSs [48, 49] but is confirmed in the fetus in only 10–40 % of these cases. In contrast, amniocentesis mosaicism is observed in only 0.3 % of cultures but, when found, is confirmed in the fetus in ~70 % of cases [50, 51]. These feto-placental discrepancies are known to occur because the chorionic villi consist of a combination of extra embryonic tissue of different sources that become separated and distinct from those of the embryo in early developmental stages. Specifically, at the 32–64-celled blastocyst, only 3–4 blastomeres differentiate into the inner cell mass (ICM), which forms the embryo, mesenchymal core of

the chorionic villi, the amnion, yolk sac, and chorion, whereas the rest of the cells become the precursors of the extraembryonic tissues [52].

The probability of mosaic or non-mosaic trisomy in the fetus itself depends on the placental lineages in which the trisomic cell line was found. CVS culture represents the villous mesenchymal core and therefore reflects the chromosomal constitution of the fetus proper to a greater extent than the direct preparation, which represent the chorionic ectoderm, farther removed from the fetus. Thus, if a mosaic chromosomal aberration is detected on both direct preparation and long-term culture, it is more likely to represent a true mosaicism of the fetus [49]. Nevertheless, in gestations involving mosaic trisomic villous mesenchyme (with or without evidence of trisomy in direct cytotrophoblast examination), it is our usual policy to further examine the fetal karyotype by amniocentesis and perform a thorough fetal ultrasound scan in order to rule out fetal malformations.

Uniparental disomy (UPD) is another adverse outcome that may be associated with CPM. In UPD, both chromosome of a given pair are inherited from a single parent, rather than one from each. UPD results when the original trisomic embryo is "rescued" by the loss of the one extra chromosome. Because in the trisomic embryos two of chromosomes come from one parent and one from the other, there is a theoretical 1 in 3 chance that the two remaining chromosomes originate from the same parent, leading to UPD. This may have clinical consequences if the chromosome involved harbors imprinted genes whose expression vary according to the parent of origin or if the two remaining chromosomes carry a mutant recessive gene, creating a homozygous state. In general, UPD has been reported for almost every chromosomal pair, although clinical consequences have been observed mainly in cases involving specific chromosomes (i.e., chromosomes 2, 6, 7, 10, 11, 14, 15, 16, 20) and depending on the parent of origin [53]. For instance, despite a relative high frequency of CPM for trisomy 2 and trisomy 7, maternal UPD (2) and maternal UPD (7) have only been reported rarely [54, 55].

A significant CPM involves chromosome 15 and is encountered in 27/100,000 samples [56]. This is associated with risk for UPD (15) which may lead to well-recognized clinical syndromes. Chromosome 15 is known to carry genes that are subject to both paternal and maternal imprinting. Maternal UPD (15), resulting from the relatively more common maternally derived trisomy 15, causes the Prader–Willi syndrome. In contrast, paternal UPD (15) caused by rescue of the less common paternal trisomy 15, results in the less frequent Angelman syndrome.

In rare cases, CPM for trisomy 15 offers the important clue that UPD may be present in the "chromosomally normal" fetus, which may be at risk of having Prader–Willi/Angelman syndrome [57, 58]. For this reason, cases in which CVS reveals trisomy 15 (either complete or mosaic) should be evaluated for UPD if the amniotic fluid demonstrates an apparently euploid fetus [56].

Early Amniocentesis

Early amniocentesis is a procedure that has come and gone. It is a first-trimester procedure, i.e., performed before 14 weeks of gestation (usually from 11+0 to 13+6) [59, 60]. Some series have included procedures as early as 9+0 weeks. Traditional amniocentesis is usually performed after 15+0 weeks of gestation; invasive procedures between 14+0 and 14+6 are usually considered early and have been included in some series but not others [61]. Since 1987, various sized observational studies on EA reported rates of procedure-related fetal loss from 1.4 to 8.1 % (see Table 20.1). Early series concluded that EA is an appropriate technique for early diagnosis but is associated with an increased fetal loss rate [62, 63]. Assel et al. [64] compared EA with mid-trimester amniocentesis and found a significant increased post procedure fetal loss rate (1.8 % vs. 0.4 %) [65].

A prospective partially randomized study by Nicolaides et al. [66, 67] showed a higher rate of fetal loss after EA compared with CVS (4.9 % vs. 2.1 %), which was significant for pregnancies at 10–11 weeks but not significant for the 12–13 weeks gestation period.

The CEMAT study compared EA between 11+0 and 12+6 weeks with standard amniocentesis (15+0–16+6). This multicenter randomized trial reporting on 1916 EA procedures showed an increased total pregnancy loss (preprocedure and post procedure losses including intrauterine and neonatal deaths) with the EA procedure (7.6 % vs. 5.9 %; $P=0.012$) [68].

Post-procedure Amniotic Fluid Leakage

Besides fetal loss, additional complications have been reported as being directly related to EA procedures. Leakage of amniotic fluid after EA is concerning because of the risk for infection, miscarriage, preterm labor/delivery, and fetal neonatal complications. The reported incidence varies from 0 to 4.6 %. For example, the CEMAT study reported an increased rate of fluid leakage that was statistically significant before 22 weeks of gestation, when EA were compared with standard amniocentesis (3.5 % vs. 1.7 %) [68]. Many reports, however, have associated EA and congenital abnormalities. The lower limb extremities have increased susceptibility with temporary disturbances from a diminution in intra-amniotic volume [69]. Second trimester procedures do not have any such association [70]. However, the CEMAT [68] trial and several others showed a significant increased rate of a foot anomaly (1.3 % vs. 0.1 %; $P=001$) for EA from 11+0 to 12+0 week. Tharmaratnam et al. [71] reported a rate of fixed flexion deformities of 1.6 %. They showed a positive association with the amount of amniotic fluid removed and the rate of musculoskeletal deformities [71].

An international randomized trial of late first-trimester invasive prenatal diagnosis to assess the safety and accuracy of amniocentesis and TA-CVS performed at 11–14 weeks was reported [47]. A fourfold increase in the rate of talipes equinovarus was observed in cases where early amniocentesis was the technique used. The authors concluded that amniocentesis at, or before, 13 weeks carries an increased risk for this specific limb defect and an additional increase in early, unintended pregnancy loss. In another study, Alfirevic et al. [72] have analyzed 14 randomized studies from the Cochrane Pregnancy and Childbirth Group Trials Registry and from the Cochrane Central Registry and Control Trials, in order to assess the safety and accuracy of the various invasive procedures employed for early prenatal diagnosis. Based on their results, they concluded that early amniocentesis is not a safe alternative to second trimester amniocentesis because of increased pregnancy loss (relative risk 1.29), and higher rates of talipes equinovarus (relative risk 6.43). Early amniocentesis has been essentially completely abandoned as CVS is a clearly safer procedure in the first trimester and, arguably, at 14 weeks as well.

In conclusion, for first-trimester diagnosis, either TA-CVS or TC-CVS are the clinically appropriate methods. We believe utilization of both CVS methods is necessary to have the most complete, practical, and safe approach to first-trimester diagnosis. EA carries a significant risk for fetal loss and fetal malformations. We have not found a situation in which EA was the appropriate method for a patient in about 20 years.

Fetal Reduction

Fetal reduction (FR) has changed considerably over the last 25 years since we first published on the subject [15, 73]. These changes have taken place in medical technology outcomes, patient choices, and the larger demographic and cultural shifts that are driving the pace and direction of change.

At its core, FR started out as a way of managing pregnancies in which the risks to both mother and fetuses from carrying multiple embryos were extreme. Selective termination (as it was called then) of some of the embryos to increase the viability of the remaining ones and reduce the risk of morbidity and mortality for the mother was a desperate approach to salvage the situation. As with numerous other technological changes, what began as a dominant concern with matters of life and death has eventually become accepted. Then indications transform from crisis "life and death" into issues of quality of life [74, 75].

FR was developed as a clinical procedure in the 1980s, when a small number of clinicians in both the USA and Europe attempted to reduce the usual and high adverse sequelae of multifetal pregnancies, by selectively terminating or reducing the number of fetuses to a more manageable number. The first European reports by Dumez and Oury [20], and the first American report by Evans et al. [73], followed by a further report by Berkowitz et al. [76], and later Wapner et al. [77] described a surgical approach to improve the outcome in such cases.

Multiple papers in the 1990s demonstrated that with triplets or more, there was clear improvement in reducing to twins. Numerous papers argued whether triplets had better outcomes "reduced" or not. Yaron et al. [78] compared triplets-to-twins data to unreduced triplets with two large cohorts of twins. The data showed substantial improvement of reduced twins as compared to triplets. The data from the 2001 collaborative series and others suggested that pregnancy outcomes for cases starting at triplets or even quadruplets reduced to twins at about 12 weeks do fundamentally as well as starting as twins.

Overall, statistics on reductions have improved noticeably over these past 25 years [14, 79, 80]. In the early 1990s, when half the cases were quadruplets or more, loss rates (up to 24 weeks) were 13 %. Early premature deliveries were an additional 10 %. Now, overall with decreasing starting numbers, better ultrasound, better understanding of zygosity, and a limited number of practitioners with extensive experience accounting for a high percentage of reductions, losses are overall down to about 4 %. Counseling must be tailored to specific starting and finishing numbers and the experience of the operator.

With the rapid expansion of the availability of donor eggs, the number of "older women" seeking FR has increased dramatically. In our experience, over 10–15 % of all patients we see seeking FR are now over 40 years of age, and nearly half of these are using donor eggs [14]. It would appear that as advances in care have developed for achieving pregnancies and ways of moderating the risk of older women who wish to have children, more of them are electing to do so.

As a consequence of the shift to older patients, many of whom already had previous relationships and children, there is an increased desire by these patients to have only one further child. The number of experienced centers willing to do 2–1 reductions is still very limited, but we believe, based upon improvement of outcomes, that it can be justified in most circumstances. Twins currently constitute about 25 % of the patients we see [14, 15].

For patients who are "older," particularly those using their own eggs, the issue of genetic diagnosis has become progressively more salient. In 2009, about 60 % of patients in the USA having ART cycles were over 35. Using the criteria of comparable risk to that of a 35-year-old, actually about 90 % of IVF patients are at increased risk [14, 15] (Table 20.2).

For the past decades and currently, most FR practitioners make their decisions as to which fetuses to keep or reduce by ultrasound evaluation only. In the 1980s, we performed most of our procedures between 9 and 10 weeks with decisions based principally on basic ultrasound and fetal position [73]. For those patients for whom genetic assessment was appropriate, we initially had them undergo amniocentesis several weeks later back at their home center [81]. We eventually changed to doing CVS a week after reduction to twins, and then to doing CVS the day before with FISH analysis overnight. In the mid-1990s, we began to have a small but increasing percentage of patients reducing to a singleton; it, therefore, seemed prudent to know

Table 20.2 Genetic risks of aneuploidy for IVF patients[a]

Factor	Risk	% of IVF cases
Advanced maternal age	>0.5 %	60
Twins or more	Age 30 × 2 = age 35	34
ICSI	1 %	66
PGD	1 % error rate	4

[a]Percentages from US Centers for Disease Control

what we were keeping before committing to it. However, waiting for a full karyotype was and is problematic for both the time interval to get results, the inconvenience of having out of town patients (half our program) having to make two trips, and the fact that others reported a 1 % mistake rate as to which was which under these circumstances [82, 83]. As FISH technology became reliable, we began routinely to do procedures on two consecutive days [14–16]. Over the last 20 years, the proportion of patients having CVS before FR has steadily risen from about 20 % in 2000 to now about 90 % of our patients [14].

There have been many papers on the true risks of prenatal diagnosis with widely diverging statistics [84]. We believe that, in multiples, the net effect in the most experienced hands is zero sum. Whatever risks there are of the diagnostic procedures are counterbalanced by the reduction of risk of loss by not, inadvertently, continuing a fetus with a serious problem who is more likely to have a spontaneous loss than a healthy one [14, 15].

An increasingly common scenario is the situation of monozygotic twins combined with one or more singletons [85, 86]. Changes in IVF culture techniques, including increasing use of blastocyst transfers, have significantly increased the incidence of monozygotic twining. Dichorionic, triamniotic triplets (DCTA), for example, have far higher rates of pregnancy loss, TTTS, and complications of prematurity [86]. The risk of TTTS is >50 %, and the risk of selective IUGR is about 20 %. As such, our approach is that if the singleton is healthy (by US and CVS), the safest thing is to reduce the twins and keep the singleton. If the singleton is not healthy, then keeping the twins is acceptable. The one thing we cannot do is reduce one of the two twins, as the risk of death or neurologic damage is as high as 12 % [87].

In the vast majority of cases, the major risk factor in determining which fetuses to keep or reduce is a chromosomal risk. However, the same principles can be applied to Mendelian risks. For example, we evaluated a couple with triplets who were both cystic fibrosis carriers. Using appropriate probes, we were able to determine that two of the fetuses were carriers, and one was affected, and was, subsequently, reduced.

As part of the FISH results, we also obtain gender. Historically, we perceived a significant bias among those patients who were interested and who mostly expressed a preference for males [87, 88]. These requests disproportionately came from patients of cultures that classically valued boys over girls. Because of such bias, we refused to let gender be a factor with the rare exception of genetic diseases with gender discordancy. Ironically, in X-linked disorders, it is the males at risk, making females the safer option.

Over the past 15 years, however, we noticed a shift to requests coming from all ethnic groups and a perceived equalization of gender preferences. In the early 2000s, our ethics consultant, John Fletcher, Ph.D., pushed us to reevaluate, and we began to be willing to consider under the following approach [16].

We prioritize FR decisions by:

1. Do we find a "problem."
2. Are we "suspicious" about anything such as somewhat increased nuchal translucency (>2 mm), smaller fetal size (such as more than ½ week, smaller gestational sac size, or placental concern);
3. If none of the above apply, then and only then, we will consider gender preference.

Patients are told that we will have a non-gender disclosing "poker-faced" discussion with them when we get the results. They will then choose which of four categories concerning gender they prefer. The groups are:

1. Those patients who want to know "everything,"
2. Those who want to know "nothing,"
3. Those who have no preference but want to know what they have kept (but not the reduced), and
4. Those who, all things considered, do have a preference (but do not want to know the reduced fetus' or fetuses' genders) [17].

Recently, we have published data that show that, now, such requests come from patients of all ethnic backgrounds and cultures [17]. When patients do have a gender preference, there is an equal preference for females as males. For patients reducing to twins, the overwhelming preference is for one of each; for those reducing to a singleton, it is essentially a 50/50 split [89].

We have also recently been able to use our technology to extend services to a group of patients not previously well served. We have in the past few years seen several gay male couples, using surrogate carriers with egg donation when both partners fertilized the eggs. The couples desired FR for the usual clinical reasons, but they requested if possible to be left with twins—one fathered by each of them. We chose to consider this request in the same vein as gender preference, i.e., only if there are no higher clinical priorities. In several cases we have been able to assess the pregnancies with CVS and ultrasound, document normal genetic results, perform paternity testing, and discover that one man fathered two and the other one. In such cases we then reduced one of the twins fathered by the same man [90].

Over the past 25+ years, data from around the globe have shown that pregnancy outcomes are vastly improved by reducing the number of fetuses in multiples. All but the most conservative of commentators have long since accepted the efficacy of FR for triplets or more. The medical data now also show that reduction of twins to a singleton clearly improves outcomes. Thus, while we expect the vast majority of patients with twins to keep them, we believe all patients with twins should be made aware of the possibility of FR. The issue then shifts to an ethical one that will never be universally accepted, but we argue that from an autonomy and public health perspective, FR needs to be seen as a necessary, but hopefully increasingly rare, procedure.

Summary

While ultrasound is an important part of prenatal diagnosis and screening, direct evaluation of fetal tissue is still required to determine almost half of genetic abnormalities. At the same time, patient's desires for privacy and the increasing possibility of significant restrictions on how far into pregnancy, a women may have reproductive choices, there is, and needs to be, an accelerated shift of definitive diagnoses into the first trimester. CVS, in experienced hands, is as safe or even safer than amniocentesis and needs to become the mainstay of diagnostic procedures.

Teaching Points

- Ultrasound cannot do everything. The combination of high quality ultrasound and diagnostic procedures performed by experienced operators is required for optimal genetic screening and diagnosis.
- Chorionic villus sampling is just as safe as amniocentesis in experienced hands.
- CVS specimens provide much more material than amniocentesis, allowing earlier procedures and faster turnaround time for diagnosis.
- Early amniocentesis (<15 weeks) should almost never be performed. It is considerably riskier than either CVS or traditional amniocentesis.
- Pre-implantation diagnosis is useful for couples at high risk for Mendelian disorders. For chromosome disorders, it does not improve take home baby rate for most couples.
- CVS or amniocentesis confirmation is still needed in PGD cases.
- CVS and fetal reduction together dramatically improve the outcome of healthy babies in multifetal pregnancies including twins.
- Genetic diagnosis before FR can provide secondary options for patients such as gender preference.

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Sonography of Pelvic Masses Associated with Early Pregnancy

21

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Clinical Implications

First-trimester sonography allows for visualization of pelvic anatomy before the expanding uterus shifts and conceals neighboring structures. For many young pregnant women, this study may be their first radiologic exam. Previously asymptomatic or small pathology hidden to palpation reveals itself to sonography and impacts subsequent clinical decisions. The sonographic findings aid in the development of differential diagnoses and are highly specific for malignancy. Incidental masses may require prompt treatment, alter the labor and delivery plan, or necessitate further imaging. The most recent joint guidelines on obstetrical sonography published by the American College of Radiology appropriately reflect the need for a comprehensive first-trimester sonogram that includes the "uterus, cervix, adnexa, and cul-de-sac region" along with the gestational contents [1]. This ensures that any poorly localized symptoms are not mistaken for the normal discomforts of pregnancy.

Undetected non-obstetrical abnormalities can cause significant complications despite their frequently benign cytology. The hormonal effects of pregnancy and increasing uterine girth can cause leiomyoma to enlarge, cysts to rupture, adnexal masses to undergo torsion, and cancers to grow. Early identification of abnormalities in the first trimester facilitates surgical treatment, if necessary, during the second trimester. At that time, risks of spontaneous abortion and preterm labor are lowest and surgical exposure remains adequate. Though smaller incidental masses with benign sonographic characteristics are amenable

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to observation [2], invasive intervention is typically initiated for those that are larger (usually greater than 7 cm in diameter), undergoing torsion, and/or suspicious for malignancy. Sonography can be used to accurately differentiate between the architectural patterns of benign and malignant masses and to determine which would be associated with an increased risk of ovarian torsion [3–6].

Techniques

Identification of incidental findings on transabdominal obstetrical sonography, inability to visualize the adnexa or cervix, or examination of an obese patient may obligate further study via the transvaginal approach [1, 3]. This technique is generally quite tolerable for the patient, eschews fetal radiation, and avoids signal attenuation by subcutaneous tissues. In addition, it provides higher resolution views of pelvic pathology owing to probes of higher frequency that contain anatomy of interest within a shallower focal length than commonly used transabdominal probes.

Three-dimensional sonography has proven particularly beneficial in imaging of the uterus and adnexa. Transvaginal probes have been adapted to collect many consecutive two-dimensional images throughout a region of interest while the probe is held stationary. This creates a user-independent, lifelike volume that can be manipulated and reconstructed in the coronal plane. This plane cannot usually be obtained by two-dimensional transvaginal sonography, but can add additional information that is essential when evaluating uterine anomalies.

Both two-dimensional and three-dimensional sonography can include color Doppler sonography. Evaluation of incidental findings must consider the local vascular tree, though physiologic hemodynamic changes of pregnancy can complicate analysis. In general, disorganized vasculature with low resistance and high flow is characteristic of ominous diagnoses [3]. Early in the first trimester, embryos are most susceptible to external teratogens, which theoretically include the thermal and mechanical energy generated by pulsed spectral Doppler, in particular [7]. Thus, the American Institute of Ultrasound in Medicine recommends utilization of Doppler studies that include the embryo or fetus only when there is clear diagnostic benefit while minimizing embryonic exposure time and intensity [8].

Uterine Masses

Fibroids

Leiomyomas, benign smooth muscle tumors commonly referred to as “fibroids,” are the most prevalent gynecologic affliction of the gravid and non-gravid female. They are commonly found incidentally on first-trimester sonography [4, 5]. These persistent, round, well-defined masses are iso- or slightly hypoechoic compared to the surrounding myometrium and demonstrate peripheral vascularity by color Doppler sonography. They may contain shadowing calcifications and areas of cystic change when undergoing degeneration (Fig. 21.1).

Fibroids are highly sensitive to estrogen, which can promote their growth and maturation in the first trimester. They may even grow so large as to overwhelm their blood supply, resulting in painful degenerative changes including changing echogenicity and loss of clear circumferential vascularity. The loss of blood supply may result in various types of degeneration: hyaline or myxoid degeneration, calcification, cystic degeneration, or red (hemorrhagic) degeneration. Red, or carneous, degeneration is a hemorrhagic infarction secondary to venous thrombosis within the periphery of the tumor or rupture of intratumoral arteries. It is of upmost importance to utilize sonography early in pregnancy to identify those fibroids that would be clinically significant due to their size and location. Submucosal fibroids may increase the risk of early pregnancy loss. If first-trimester miscarriage is eluded, these benign masses can have significant detrimental ramifications that are not realized until later trimesters. Mass effect and disruption of placental implantation caused by large fibroids compete with fetal growth and can obstruct fetal and placental delivery if located within the lower uterine segment [5, 9]. Increased pressure above a low-lying fibroid

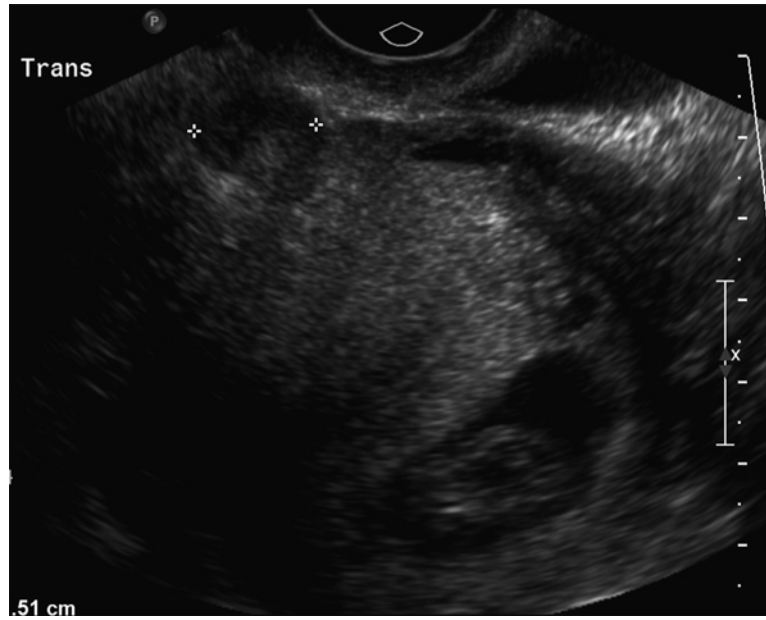

Fig. 21.1 Subserosal fibroid. Transvaginal grayscale transverse image of the uterus demonstrates a round heterogeneous mass, measuring 0.51 cm wide (+), projecting beyond the contour of the uterus. The gestational sac with embryo is noted

during labor increases the risk of uterine rupture and fetal mortality. Despite these complications, intervention is usually not necessary or commonly pursued until the postpartum period.

The pervasive fibroid can present unexpected challenges for the medical imaging specialist. Subserosal-type fibroids pushed close to an ovary by the gravid uterus can be difficult to differentiate from a solid ovarian mass. Degenerative changes in such a fibroid may further complicate diagnosis. Imaging a separate ovary, often better differentiated on three-dimensional sonography, will exclude an ovarian mass. Color Doppler may also be helpful in delineating blood flow that connects the uterus and fibroid. If ultrasound is inconclusive, further imaging with MRI may be required.

Adnexal Masses

Traditional management of adnexal masses during pregnancy has been surgical, but with surgeries come both fetal and maternal risks. The goal of ultrasound evaluation is to determine when conservative management with observation is appropriate. Simple cysts of any size and classic-appearing hemorrhagic cysts are highly unlikely to be malignant lesions in menstruating females. Follow-up or further evaluation is recommended only when the size is greater than 5 cm. Reports have shown a high accuracy of ultrasound for determination of malignant potential. Schmeler et al. and Kumari et al. reported correct diagnosis of malignancy in all pregnant patients studied presenting with incidental adnexal masses [6, 10].

Corpus Luteum

A retrospective review of sonography performed on over 18,000 pregnant patients identified a 2.3 % prevalence of adnexal masses; the majority were small (<5 cm) simple cysts that were without complication during the pregnancies [11]. The majority of these cysts likely begin as corpora lutea: the most commonly encountered cystic adnexal mass during pregnancy [4]. Corpora lutea form after fertilization of an expulsed ovum from an ovarian follicle. They endure to produce progesterone and maintain the early pregnancy. Fluid-filled with smooth, thick walls, they grow to a maximum diameter at the end of the first trimester. The decreasing functionality of the corpus luteum as the placenta assumes that an endocrinologic role is reflected sonographically by its serially shrinking size by the second trimester.

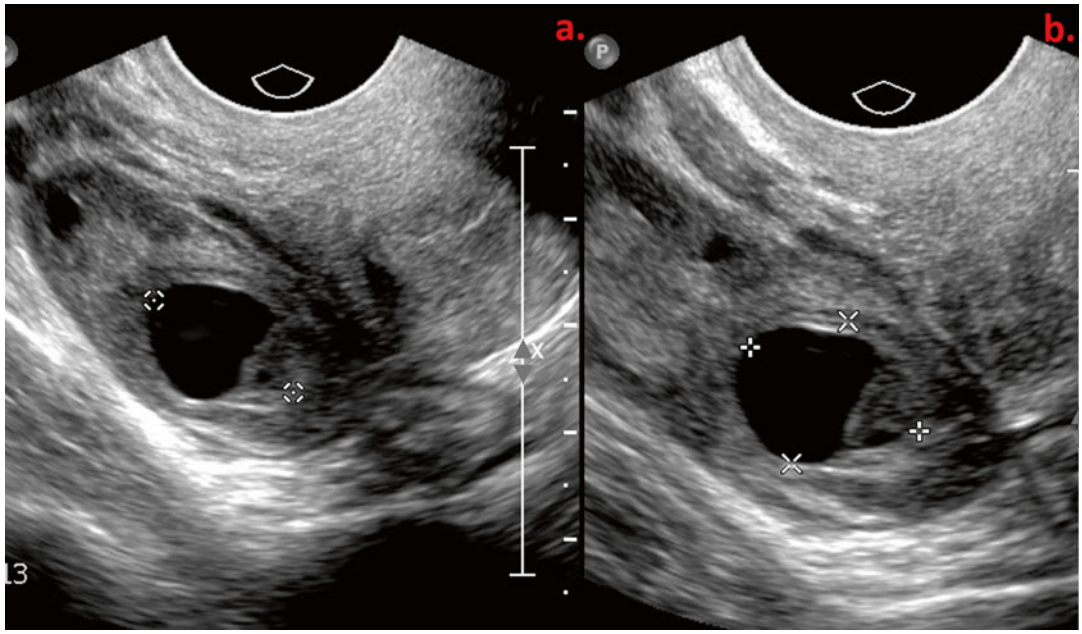

Fig. 21.2 Corpus luteum. Grayscale transvaginal (**a**) transverse and (**b**) sagittal images of the ovary demonstrate a predominately anechoic cyst containing hypoechoic dependent debris representing old blood products

The lifetime of the corpus luteum in a pregnant woman is much longer than during a normal menstrual cycle and it has more opportunity to grow; thus, complications such as rupture, torsion, and hemorrhage can more commonly occur in a pregnant patient (Fig. 21.2a, b) However, intervention and further imaging are otherwise unnecessary for this physiologic incidental finding and should not be pursued during the first trimester when progesterone production is essential.

Corpus Luteum Cysts

A persistent corpus luteum can seal externally within the ovary and continue to collect fluid within, forming a unilocular corpus luteum cyst. Because the cyst contains fluid, it is anechoic with enhanced through-transmission, though it may exhibit thin lacelike echogenic septae if it persists into the second trimester and is filled with blood [5]. The size of the cyst is a strong predictor of its ability to spontaneously regress, with almost all cysts under 5 cm in diameter resolving completely without intervention [12]. The most recent guidelines (2010) for non-gravid women from the Society of Radiologists in Ultrasound do not recommend follow-up sonography for simple cysts smaller than 5 cm, whereas yearly sonography of larger cysts should be considered, despite low malignant potential [13]. Standard scheduling of obstetric ultrasounds offers the opportunity to track the growth of corpus luteum cysts throughout pregnancy.

Both the corpus luteum and corpus luteum cyst have distinguishing dense peripheral "ring of fire" vascularity on color Doppler imaging (Fig. 21.3a–c). These vessels exhibit low resistance and high diastolic flow on spectral Doppler. There are typically little or no internal solid components. Ectopic or heterotopic pregnancies in the adnexa imitate corpus luteum cysts because they, too, are fed by a peripheral ring of vessels and can be seen directly adjacent to a cyst (Fig. 21.4a, b). The critical distinction is made by determining if the adnexal mass is para- or intraovarian. Ectopic pregnancies should move independently from the ovary with pressure applied

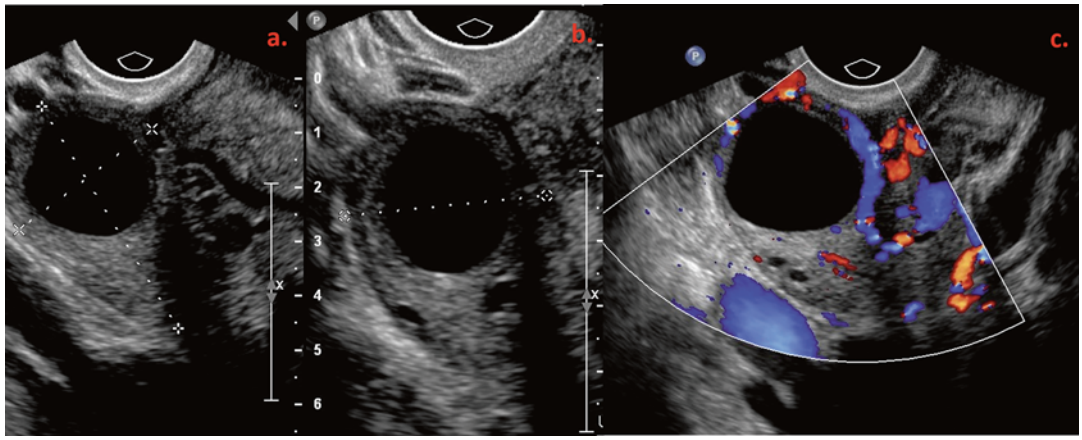

Fig. 21.3 Corpus luteum cyst of pregnancy. Transvaginal (**a**) sagittal and (**b**) transverse grayscale images of the ovary demonstrate an anechoic round structure with thin walls. (**c**) Sagittal color Doppler image demonstrates peripheral vascularity representing the "ring of fire"

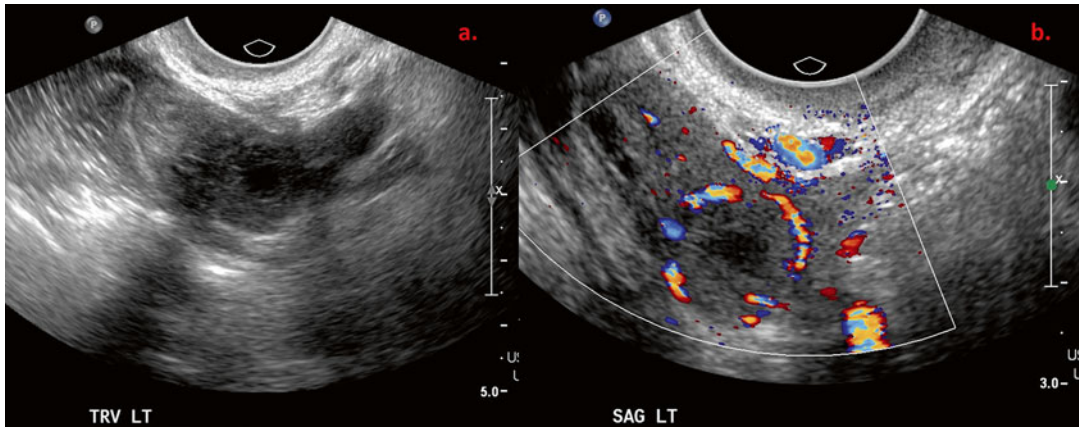

Fig. 21.4 Ectopic pregnancy. (**a**) Transverse view of the left adnexa depicting a thick, echogenic ring and (**b**) peripheral vascularity on sagittal color Doppler

by the examiner. This "sliding sign" is not visualized during examination of intra-ovarian corpus luteum cysts, which remain coordinated in movement with the ovary. In a retrospective study of 78 pelvic sonograms performed on women exhibiting symptoms consistent with ectopic pregnancy during the first trimester, the radiologists were able to correctly identify ectopics in 23 of 27 patients exhibiting the "sliding organ sign." Although not a strong differentiator, ectopic pregnancies also tend to be more complex and echogenic than luteal cysts when compared to the ovarian parenchyma [14].

Corpus luteum cysts are usually asymptomatic, especially when they are relatively small in size, as opposed to ectopic pregnancies that will invariably become symptomatic. However, large cysts can rupture, undergo torsion, and bleed [12]. Intervention is imperative for ectopic pregnancies and recommended for cysts and benign masses greater than 7 cm, but not recommended for small luteal cysts [13].

Hemorrhagic Corpus Luteum Cysts

The clinical presentation of a hemorrhagic corpus luteum cyst is characterized by more unilateral pain than its predecessors. The resolution of pain does not correlate with resolution of the hemorrhagic cyst, which can evolve over subsequent months [15]. Sonographically, the acute phase of the hemorrhage demonstrates very hyperechoic internal echoes (Fig. 21.5a, b). As the blood settles, the cyst appears more heterogeneous with thin, fibrinous septations that are without color Doppler flow. The clot retracts to the walls of the cyst, appearing as a solid or reticular hyperechoic structure. Throughout this course, the cyst should always remain well defined with enhanced through-transmission owing to the predominant presence of non-bloody cystic fluid. If the cyst is not intact and the patient is symptomatic, a diagnosis of rupture is supported by the presence of free pelvic fluid.

Due to the lack of specificity observed in some hemorrhagic corpus luteum cysts, follow-up imaging may be appropriate. Growth requires continued surveillance. The presence of thick septations and nodular walls, especially when there is associated vascularity, is suspicious for neoplasia and surgical intervention must be considered. Alternatively, magnetic resonance imaging may be helpful for further characterization (Fig. 21.6a–c). By the second-trimester anatomy scan, true functional hemorrhagic cysts should have involuted.

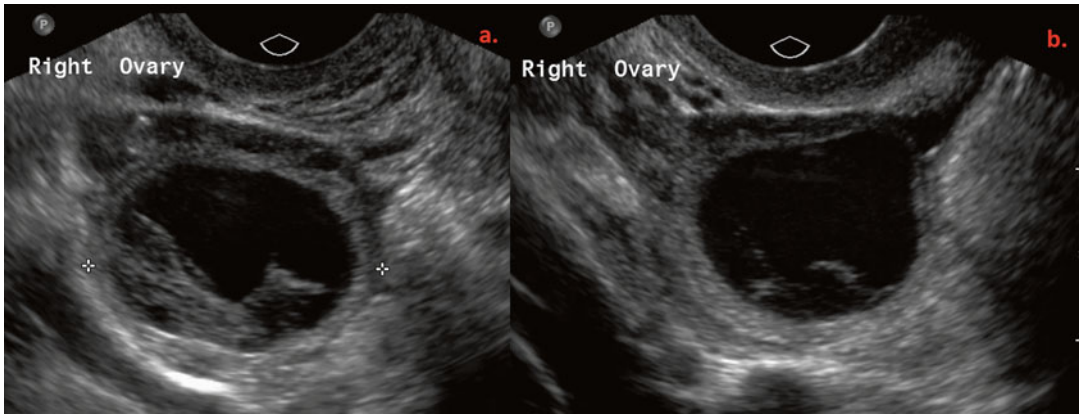

Fig. 21.5 Hemorrhagic corpus luteum cyst of pregnancy. Grayscale transvaginal (**a**) transverse and (**b**) sagittal images of the ovary show heterogeneous echogenic material within an anechoic cyst representing hemorrhagic blood products in a corpus luteum cyst

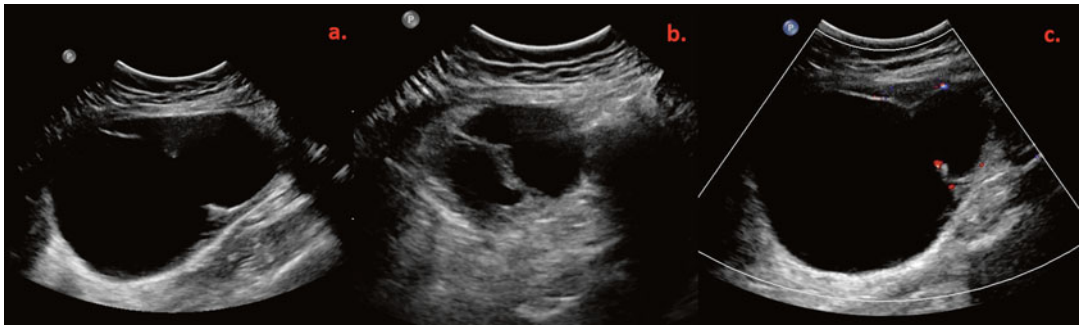

Fig. 21.6 Borderline mucinous tumor of the ovary. Transabdominal grayscale (**a**) sagittal and (**b**) transverse images of the ovary demonstrate a predominately cystic mass with thick septations. (**c**) Color Doppler imaging demonstrates blood flow within a septation

Decidualized Endometriomas

Sonography has both high diagnostic sensitivity and specificity for endometriomas, most commonly implanted within the ovaries. These round, hypoechoic cystic masses have a characteristic sonographic appearance with regular thick walls and possibly small echogenic foci along the inner rim. Within the endometrioma, homogenous low-level echoes can resemble a hemorrhagic corpus luteum cyst; however, the latter will involute by the second trimester and the former will not (Fig. 21.7). Just as the endometrium of the uterus decidualizes under the influence of progesterone during pregnancy, about 12 % of ovarian endometriomas also undergo decidualization [16]. Their benign appearance transforms to closely mimic borderline ovarian tumors (Fig. 21.8a, b). They can rapidly develop solid intracystic papillary excrescences and irregular walls. The projections may be quite vascular and can exhibit low resistance flow. Because ovarian endometriomas

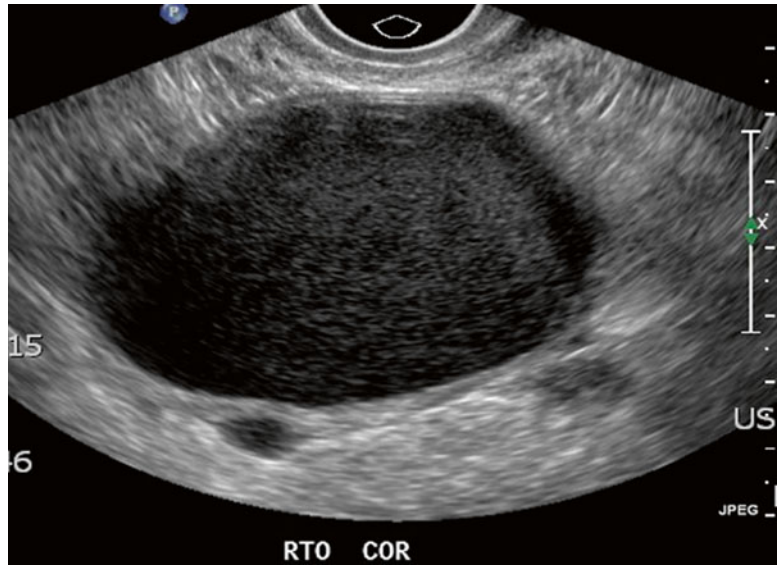

Fig. 21.7 Endometrioma. Transvaginal coronal image of the right adnexa demonstrates a large, thick-walled hypoechoic mass with homogeneous internal echoes

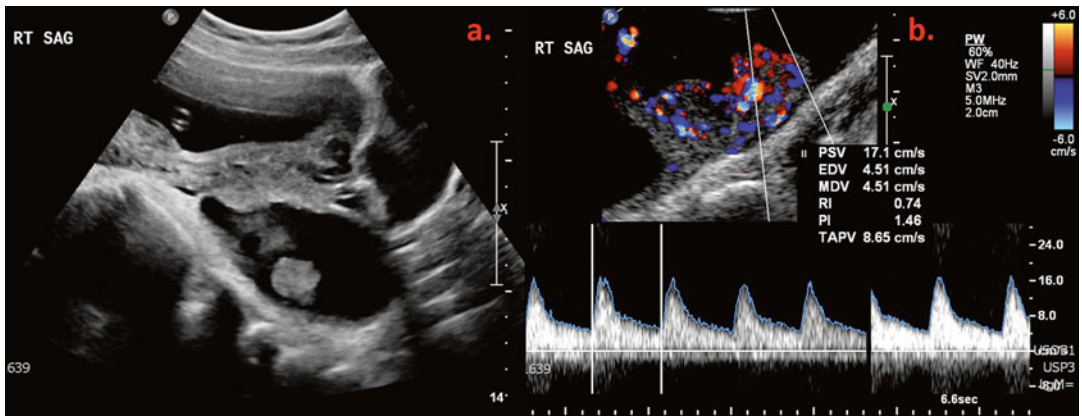

Fig. 21.8 Decidualized ovarian endometrioma mimicking a borderline tumor. (**a**) Sagittal image of the right adnexa shows a cystic mass with internal irregular solid projections. Seventeen-week IUP is visible. (**b**) Color Doppler imaging demonstrates low-resistance vascularity within the excrescences

are more likely to undergo malignant transformation than extragonadal types, though uncommon in reproductive-age women with small endometriomas, the correct diagnosis is crucial and particularly complicated during pregnancy.

Though the concerning features of decidualized endometriomas tend to revert after delivery, most women elect for surgical removal while pregnant [16], thus incurring the risks that accompany such intervention. Sonography remains the best modality to characterize ovarian masses in the hopes of distinguishing decidualized ovarian endometriomas from malignant tumors, though the task remains difficult. Most notably, endometriomas tend to become slightly smaller or remain stable in size throughout pregnancy, while cancerous masses enlarge. Sonographic appearance of the wall of an endometrioma should be similar to that of uterine endometrium. MRI does not add significant diagnostic benefit and is limited by avoidance of contrast, but may assist in further comparison of endometrial tissues or ruling out a hemorrhagic corpus luteum cyst. Analysis of vascularity has not revealed consistent chronological, morphological, or flow differences [17]. If surgical intervention is deferred, monthly sonographic follow-up is recommended [17].

Dermoid Cysts

Although "dermoid cyst" is the term used most commonly, the correct medical nomenclature for these tumors is "mature teratoma." Sonography is a valuable modality for diagnosing benign ovarian dermoid cysts. In a prospective study of 1066 sonograms of adnexal masses, radiologists correctly identified dermoid cysts 86 % of the time and never misdiagnosed them as malignant [18]. An older study of second- and third-trimester sonography of 131 adnexal lesions greater than 4 cm in diameter correctly identified 95 % of the dermoids [2]. Advances in transvaginal ultrasound technology and changes in prenatal screening since publication of the latter study have led to improved early detection of smaller dermoids. This is important given that they are the most common complex pelvic mass identified during pregnancy and would otherwise go undiagnosed until much later in 10 % of women with dermoids [4, 5].

The accuracy of experienced medical imaging experts is especially impressive considering the wide array of appearances that dermoid cysts exhibit (Figs. 21.9, 21.10a, b, and 21.11a, b). Nearly universally, dermoids are well-circumscribed complex heterogeneous masses arising from the ovary.

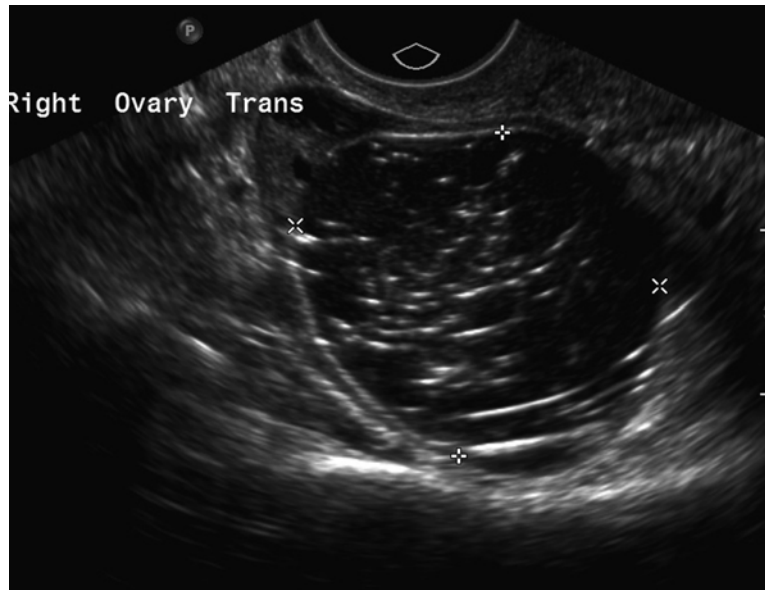

Fig. 21.9 Dermoid. Transvaginal grayscale transverse images of the ovary demonstrate a heterogeneous round mass with punctate and linear echogenic foci representing strands of hair

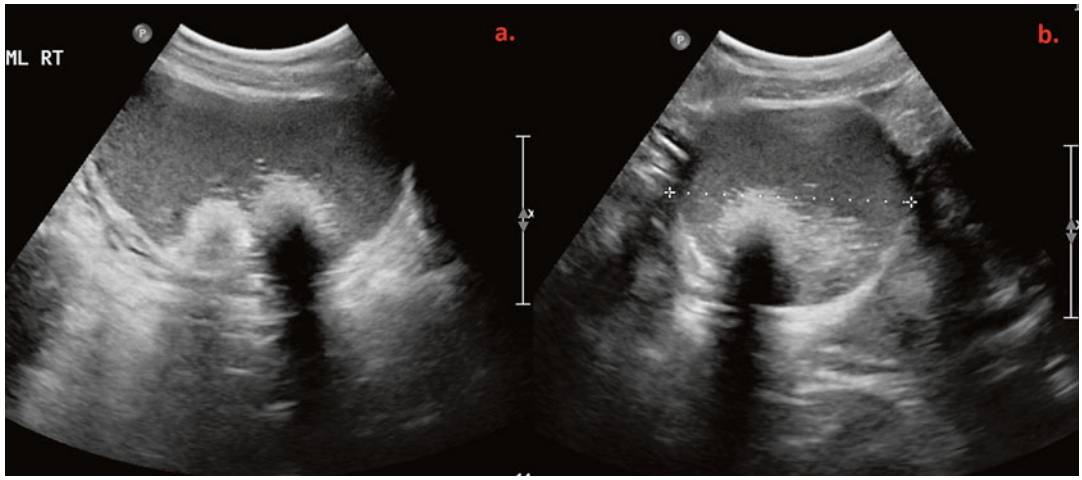

Fig. 21.10 Dermoid cyst. (**a**) Sagittal and (**b**) transverse grayscale images of the ovary demonstrate a predominately homogenous mass with echogenic areas and posterior acoustic shadowing from calcifications

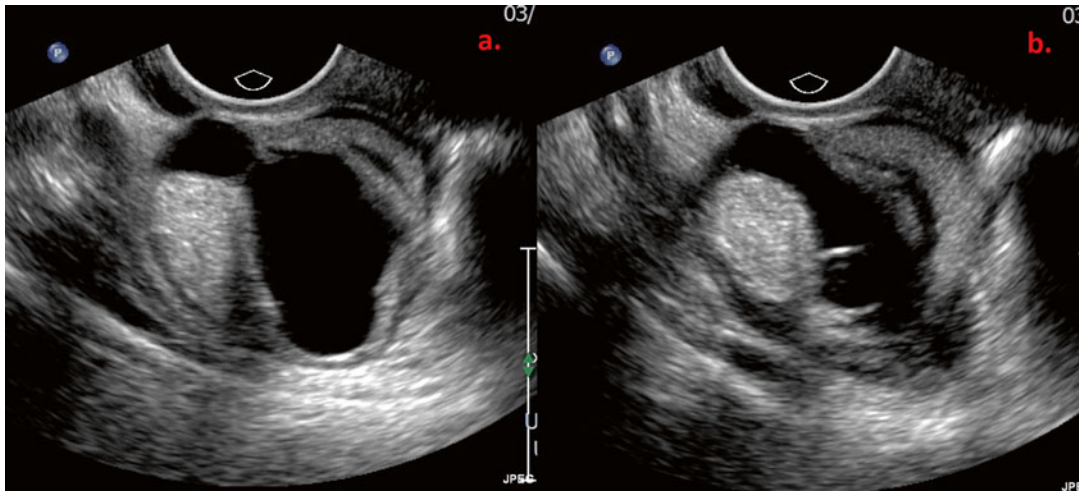

Fig. 21.11 Mature cystic teratoma and Brenner tumor. Grayscale transvaginal (**a**) sagittal and (**b**) transverse image of the ovary demonstrates a heterogeneous mass with mixed anechoic cystic and solid echogenic components

They consist of well-differentiated tissues from multiple germ cell lineages (e.g., fat, calcifications, hair, and sebum), creating distinctive hyperechoic linear markings (lines and dots) within the dermoid and highly echogenic areas that strongly shadow ("tip of the iceberg sign"). This appearance may be mistaken for nearby gas-containing bowel that only allows visualization of the surface closest to the transducer. Although less common, fat-fluid levels and balls of sebum are nearly pathognomonic for dermoid cysts.

Benign cystic teratomas will not change in size under the influence of pregnancy, but are well-known perpetrators of ovarian torsion in expectant mothers [5]. The ovary will exhibit limited venous outflow on color Doppler with free pelvic fluid from edema and vascular congestion. The main ovarian vessels may appear twisted and some flow to the ovary from uterine collaterals can be present. The patient may experience repeated episodes of clinical improvement followed by pain as the torsion temporarily

resolves and resumes, respectively; thus, the torsion may not be captured on a single sonographic study. Pedunculated dermoid cysts are particularly prone to torsion and subsequent rupture, themselves, and can present with an acute abdomen [12]. In these cases, surgery should be pursued, as necrosis and peritonitis may develop. Otherwise, conservative observation for small dermoids is appropriate.

Ovarian Cancer

It is estimated that 3.6–6.8 % of all persistent adnexal masses seen on prenatal sonography are malignant [3]. It is reassuring that the overall prevalence of adnexal masses in pregnancy is low, but the few cancers that exist are definite "do-not-miss" diagnoses. First-trimester sonography presents an opportunity for early detection of a cancer that is otherwise asymptomatic and, thus, diagnosed at advanced stages. As commented above in prior sections, ultrasound has shown high accuracy for determination of malignant potential, although a benign mass may occasionally mimic a cancerous mass. If sonographic findings are indeterminant, MRI may add specificity, but may also be limited by the restricted use of gadolinium contrast in the pregnant patient.

Tumor markers associated with gynecologic cancers are physiologically elevated during pregnancy. CA-125 remains the best laboratory test for ovarian cancer in non-gravid females despite variable elevations in only half of women with stage I disease [3]. However, healthy pregnant women have high CA-125 levels that peak at an average of 55 U/mL (upper limit of normal 35 U/mL) during the first trimester [19]. CEA, AFP, and beta-hCG levels increase, as well. Thus, imaging remains the best diagnostic tool for ovarian cancer in pregnancy.

The US Department of Health and Human Services published a systemic review of 14 years of literature comparing the ability of multiple imaging modalities to differentiate benign from malignant adnexal masses. The report concluded "there is no evidence to support the superiority of any single modality" for this purpose, claiming that ultrasound, MRI, and CT are nearly equivalent while FDG-PET falls short [20]. However, interpretation of sonography by experienced imaging specialists using criteria proposed by the International Ovarian Tumor Analysis study remains superior to tumor markers and mathematical predictive models [21]. In the pregnant patient, this safe and minimally intrusive modality is a logical first step.

The ultrasound examiner must first confirm that the suspicious mass is intraovarian by probing with the transvaginal transducer and observing the absence of "sliding." Vigilance is piqued by large, complex adnexal masses [11]. Several simplified scoring systems exist to quantify the likelihood of malignancy based on a holistic assessment of mass morphology [3]. Thick, irregular septations within the mass and mural nodules or papillary excrescences are highly concerning. Serous cystadenocarcinoma exhibits more anechoic areas than the mucinous type, but never exists as a unilocular cyst [5, 12]. However, careful evaluation of the entire cyst wall is very important because the borderline serous or mucinous cystadenocarcinoma may be almost completely unilocular, with the exception of one or more mural nodules that usually demonstrate associated vascularity by color Doppler (Fig. 21.12a, d).

Solid masses may represent metastasis, commonly from the GI tract (i.e., Krukenberg tumor), or primary solid tumors of the ovary. These have a wide range of sonographic appearances, though predominantly solid tumors with few cystic components generally represent the poorest prognoses. Solid tumors are divided into epithelial, germ cell, and sex cord/stromal types with distinct epidemiology aiding diagnosis. Epithelial ovarian tumors, including cystadenocarcinomas, are the most common ovarian cancers, largely affecting postmenopausal women. On the opposite end of the spectrum are the germ cell tumors, including teratomas, which tend to afflict younger women. Sex cord/stromal tumors (i.e., fibromas, thecomas, granulosa cell tumors) are sometimes associated with familial syndromes and appear in middle age.

Generally, when color Doppler is applied to solid components of malignant neoplasms, increased disorganized vascularity is revealed. Spectral Doppler may demonstrate low resistive and pulsatility indices, representing high blood

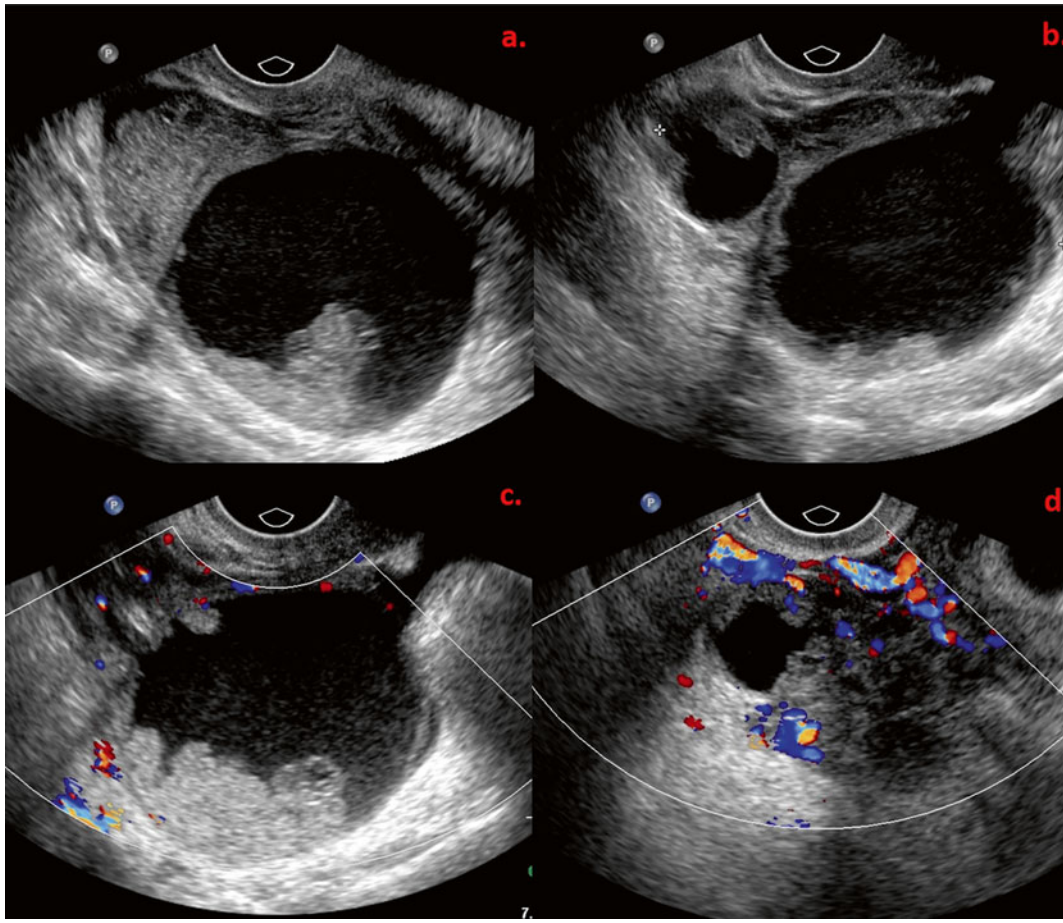

Fig. 21.12 Serous borderline tumor. Grayscale transvaginal (**a**) sagittal and (**b**) transverse images of the ovary demonstrate a large hypoechoic cystic mass with hyperechoic papillary projections. Color Doppler images (**c**, **d**) demonstrate mild vascularity within the papillary projections as well as a second lesion with moderate vascularity

flow to the tumor. Free fluid in the abdomen is likely indicative of maternal ascites from tumor spread. Surgical removal of suspicious masses is recommended in order to protect the patient and fetus. When performed in the second or late first trimester, complication rates are low and most babies will be delivered at term.

Abdominal Mimickers

Appendicitis can present similarly to complicated right-sided adnexal masses due to its location near the right ovary. Classically, acute epigastric pain shifts to the right lower quadrant and is associated with nausea, vomiting, and anorexia. Throughout pregnancy, the enlarging uterus forces the appendix slightly higher than McBurney's Point (normally located one-third of the distance on an imaginary line from the right anterior superior iliac spine to the umbilicus), but this change is not significant during the first trimester. Pregnant women are also more likely to present with digestive or urinary complaints than nonpregnant women, which can mimic normal pregnancy symptoms.

CT is often utilized for diagnosis of acute appendicitis in nonpregnant women. However, in those who are pregnant and presenting with right-sided pain, sonography is an excellent alternative

to avoid radiation. MRI can also be used as a problem-solving tool when ultrasound is indeterminate. The inflamed appendix appears as a large (greater than 6 mm), fusiform, blind-ending structure with thick, hyperemic walls. The appendix will be noncompressible and, in cases of rupture, surrounded by a small amount of fluid. Sometimes, a hyperechoic appendicolith is discovered occluding the appendiceal lumen.

If the appendix has ruptured, the wall will not be intact, allowing fluid (e.g., feces, pus) to collect at the opening. If it does not remain localized, the noxious fluid can irritate the uterus, resulting in higher rates of preterm labor and fetal loss. This is further exacerbated by delayed operative intervention in pregnant women. A sonographic work-up for appendicitis must exclude ectopic/heterotopic pregnancies and ovarian torsion if the patient presents in the first trimester and abruption in the third trimester. Pyelonephritis and round ligament pain remain clinical diagnoses.

Pregnancy induces changes in the urinary system, including dilation of the ureters and collecting systems. Right pelvocaliectasis and ureterectasis are more prominent due to dextrorotation of the enlarging uterus, although hormonal influences on the smooth muscle of the ureter can cause fullness bilaterally. Previously asymptomatic ectopic kidneys lying low in the pelvis can cause displaced "flank" pain from vesicoureteral reflux and ascending urinary tract infections. The pain can mimic an adnexal origin. Sonography will likely show hydronephrosis in a pelvic kidney located near an ovary, with infection confirmed by urinalysis.

Summary

A comprehensive sonographic examination of the pelvis in the first trimester can reveal a spectrum of incidental findings that share their space with a growing uterus. Though most of the pathology discussed in this chapter is also encountered in non-gravid females, the unique hormonal environment of pregnancy can instigate complications or cause otherwise benign-appearing masses to look suspicious. Sonography remains the superlative modality for examination of the adnexa and for distinguishing malignant from benign masses, thus allowing pursuit of early intervention when safest during the pregnancy or if complications such as torsion are deemed likely. Its role during pregnancy surpasses tumor markers and can help clarify the physical exam, which is confounded by shifting anatomy. Sonography is also superior for ascertaining the hazards of uterine fibroids, a potentially serious roadblock to implantation, fetal growth, and later delivery. Sonography's vital role during early pregnancy will continue to grow with increased utilization of three-dimensional images.

Teaching Points

- First-trimester sonography leads to earlier detection of small masses that would otherwise go undiagnosed until symptomatic or at an advanced stage. Early exams should cover a comprehensive inspection of the pelvis.
- Regularly scheduled obstetric sonography offers the opportunity to follow up and track first-trimester incidental findings for growth or complications.
- Though most pelvic masses identified in the first trimester are benign, malignancy is occasionally seen. Sonography in conjunction with color Doppler can help make this distinction.
- Fibroids are the most common gynecological masses in gravid and non-gravid women, alike. Two- and three-dimensional sonography can both be useful for localizing and measuring fibroids to determine if they will present challenges during pregnancy and labor.
- Sonography has high accuracy in the characterization of adnexal masses and determining their potential to undergo torsion. This can be very helpful during pregnancy, a time when cysts are more likely to rupture or hemorrhage and cystic or solid masses have more opportunity to be a fulcrum for ovarian torsion.
- Sonography remains superior to tumor markers for ovarian cancer detection during pregnancy.

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