Pearls and pitfalls in the diagnosis of ectopic pregnancy

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Authors: S. Ramanathan¹, P. Nepal¹, D. Kumar¹, Y. Palaniappan², S. B. Ladumor³, H. Hena¹, M. Khanna¹, N. salah ahmed mohamed¹, A. Choyi madathil¹, A. SHEIKH⁴, M. Heidous¹; ¹Doha/QA, ²Puducherry/IN, ³Doha,Qatar, Doha/QA, ⁴Ottawa, ON/CA
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Learning objectives

1. To review the incidence, risk factors and clinical presentation of ectopic pregnancy
2. To review the role of Beta-hCG, discriminatory levels and pattern of rise in ectopic pregnancy
3. To describe the sonographic features of normal intrauterine pregnancy
4. To review the spectrum of sonographic features of tubal and nontubal sites of ectopic pregnancy
5. To familiarize the imaging features of potential mimickers of ectopic pregnancy.
6. To summarize the various pearls and pitfalls in the diagnosis of ectopic pregnancy.
Background

Introduction:

Abnormal implantation of the blastocyst outside the uterine endometrium constitutes ectopic pregnancy (EP). Various implantation sites include tubal (ampulla isthmus, fimbria, and interstitial) and

Abnormal implantation of the blastocyst outside the uterine endometrium constitutes ectopic pregnancy (EP). Various implantation sites include tubal (ampulla isthmus, fimbria, and interstitial) and non tubal (cornual, ovarian, cervical, abdominal pregnancies and previous cesarean scar). Signs and symptoms can vary from pelvic pain or vaginal bleeding to death from massive intraperitoneal haemorrhage.

Incidence and risk factors:

EP accounts for approximately 2% of all pregnancies and it remains the leading cause of death during the first trimester of pregnancy, with a 9%-14% mortality rate. The main risk factors include a history of ectopic pregnancy, tubal surgery, and pelvic inflammatory disease [1].

Clinical presentation: Most patients who have an EP present with a 5-9-week history of amenorrhea, mild pelvic pain, and vaginal spotting. More than half of the patients who have an EP are asymptomatic. Therefore, it has now become a routine to document intrauterine pregnancies for all patients in their first trimester.

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Quantitative measurement of serum human chorionic gonadotropin (hCG) and transvaginal ultrasound (TVS) are the first two steps in a suspected EP.

PEARLS AND PITFALLS IN BETA-HCG MEASUREMENT

The third International Standard (IS), or the first International Reference Preparation, is the most widely used standard of measurement of Beta-hCG. Many institutions still use the second IS which can be converted to the International Reference Preparation by multiplying by a factor of 1.8. So it is important to be aware of measurement standard in your institution [2].
- HCG doubles every 2 to 3 days and it decline after 8 weeks. HCG and mean sac diameter (MSD) increase proportionally until the 8th week.

- The discriminatory level of Beta-hCG: the level above which an imaging scan should reliably visualize a gestational sac (GS) within the uterus in a normal intrauterine pregnancy (IUP) is: 2000 mIU/mL for transvaginal ultrasonography (TVS) and 6000-6500 mIU/mL for a transabdominal ultrasonography (TAS). These values should be used as guidelines and not absolute threshold.

- No single serum Beta-hCG level is diagnostic of an EP. Serial levels are necessary to differentiate between normal and abnormal pregnancies and to monitor resolution of EP once therapy has been initiated. Serial measurements can be used to evaluate pregnancy of unknown location (PUL).

- Pattern of beta-hCG in EP: Serum hCG levels often rise at a much slower rate. If -hCG levels increase by less than 50% during a 48-hour period, there is almost always a nonviable pregnancy either intra- or extra uterine. 85% of viable IUP show -hCG rise by 66% or more during a 48-hour period. However, up to 21% of EP demonstrates a -hCG doubling time identical to that of IUP. Arriving at a -hCG plateau early in the pregnancy is highly suggestive of an EP [3].

Table 1: Pattern of Beta-hCG in various conditions

<table>
<thead>
<tr>
<th>Serial Beta-hCG</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doubling</td>
<td>Normal IUP</td>
</tr>
<tr>
<td>Rising too slow</td>
<td>EP, abnormal IUP</td>
</tr>
<tr>
<td>Plateaus</td>
<td>abnormal IUP, retained products of conception, EP</td>
</tr>
<tr>
<td>Decreasing</td>
<td>abnormal IUP, SAB, non viable EP</td>
</tr>
</tbody>
</table>
Findings and procedure details

NORMAL INTRAUTERINE PREGNANCY (IUP) [4, 5, 6, 7]

Gestational sac (GS) Fig. 1 on page 15:

- Filled with chorionic fluid
- Intradecidual sign - small collection of fluid that is eccentrically located within the endometrium and is surrounded by a hyperechoic ring
- Double decidual sign- Two concentric echogenic rings that has been termed the double sac sign or double decidual sign formed by decidua parietalis (hyperechoic), fluid in the uterine cavity (hypoechoic)and decidua capsularis (hyperechoic)
- Doppler- detection of peritrophoblastic flow. Intradecidual PSV>= 15cm/sec & RI <=0.55

Yolk sac

- 1st structure to be seen in GS
- TVS- always seen when MSD 8mm
- TAS- always at MSD 20mm
- Diagnostic of IUP
- No longer detected by end of 1st trimester

Embryo

- TVS- embryo with CRL of 1-2 mm
- Cardiac activity - as early as 6 weeks
- Amnion - seen as early as 5.5 wk
- Double bleb sign- early sign of amnion formation. It refers to the presence of an amnion and yolk sac at 5 to 6 weeks. The embryo lies between these two structures
- Visualization of amnion in absence of embryo- intrauterine embryonic death
Table 2: Correlation between TVS visualization and gestational age

<table>
<thead>
<tr>
<th>Stage of development</th>
<th>G age (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G sac</td>
<td>5</td>
</tr>
<tr>
<td>G sac &amp; Y sac (No embryo/ cardiac activity)</td>
<td>5.5</td>
</tr>
<tr>
<td>G sac &amp; Y sac (living embryo CRL&lt;5mm)</td>
<td>6</td>
</tr>
<tr>
<td>Embryo &gt;5mm</td>
<td>Based on CRL</td>
</tr>
</tbody>
</table>

Adnexa Fig. 2 on page 15:

- Corpus luteum cyst is a normal feature of pregnancy.

- Variable sonographic appearance: simple cyst, thick walled cyst, complex cyst or homogeneous solid appearance. It mimics EP and can show “ring of fire”, on color Doppler.

- To determine if a mass arises from the ovary gentle pressure can be applied to the adnexa. If the mass moves with the ovary it is more likely to be a corpus luteum as ovarian EP is very rare (1%). If the mass moves separately from the ovary it is extra ovarian and probably an EP.

EARLY PREGNANCY FAILURE

- CRL >5 mm and no cardiac activity

- MSD # 8 mm and no yolk sac

- MSD # 16 mm and no embryo

- Absent yolk sac in presence of an embryo

- Absent cardiac activity in embryo seen by TAS. If early, need to confirm with TVS.

SONOGRAPHIC FEATURES OF EP

Tubal pregnancy is the commonest form of EP seen in 95% of cases and various sonographic features have been described for confident diagnosis [8, 9].
A. Fallopian tube  
Fig. 3 on page 16  
Fig. 4 on page 16  
Fig. 5 on page 17 :

· An adnexal mass that is separate from the ovary is the most common finding of a tubal pregnancy seen in up to 89%-100% of patients. Associated yolk sac, living embryo and independent movement form the ovary increases the specificity. However, an extra uterine mass may not be detected at transvaginal US in 15%-35% of patients with an EP.

· The tubal ring sign is the second most common sign of a tubal pregnancy. The tubal ring sign describes a hyperechoic ring surrounding an extra uterine gestational sac.

· A related finding is the "ring of fire" sign, which is recognized by peripheral hypervascularity of the hyperechoic ring. It is a nonspecific finding and may also be seen in a normal maturing follicle or a corpus luteal cyst. Determining the location of this type of flow, whether it is within the ovary or outside the ovary, is most important to distinguish between an EP and a corpus luteum. This sign is most helpful when no definite EP is seen on gray-scale images. Color Doppler images of the adnexa may demonstrate the ring of fire flow in an otherwise nondescript adnexal lesion and thereby may improve confidence in the diagnosis of ectopic pregnancy.

B. Ovary:

Corpus luteum is the most common finding in the ovary. About 80% of EP is found on the same side as the corpus luteum. Contralateral implantation occurs in up to one-third of cases.

C. Uterus  
Fig. 6 on page 17 :

Intrauterine findings of an ectopic pregnancy include

1. Normal endometrium

2. Pseudo-gestational sac - represents a thick decidual reaction surrounding intrauterine fluid. 10% of EP demonstrates a pseudo-gestational sac.

3. Trilaminar endometrium - Normally seen in late proliferative phase of the normal menstrual cycle. Absence of a true GS in the presence of a trilaminar endometrium on US images is highly suggestive of an EP.

4. Thin-walled decidual cyst - is found at the junction of the endometrium and the myometrium. It can be seen in both normal and abnormal pregnancies. The thin wall of the decidual cyst differentiates it from a true GS [10, 11].
### Table 3: Difference between true and pseudo gestational sac

<table>
<thead>
<tr>
<th>US features</th>
<th>Intrauterine GS</th>
<th>Pseudo sac</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shape</strong></td>
<td>Round</td>
<td>Ovoid</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Eccentric</td>
<td>Central</td>
</tr>
<tr>
<td><strong>Margins</strong></td>
<td>Well defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td><strong>Decidual reaction</strong></td>
<td>Well defined</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Single / double sac</strong></td>
<td>Double decidual sac sign</td>
<td>Single layer</td>
</tr>
<tr>
<td><strong>Doppler US</strong></td>
<td>High velocity, low resistance peritrophoblastic flow</td>
<td>Sparse flow with PSV &lt;6 cm/s with no end diastolic flow</td>
</tr>
</tbody>
</table>

### D. Extra uterine Fig. 7 on page 18:

- Extra uterine findings of EP include pelvic free fluid, hematosalpinx, and hemoperitoneum.
- Pelvic free fluid is seen in 50-75% of EP and does not necessarily imply tubal rupture. Non specific fluid is also detected in 20% of all IUP.
- Pelvic hemorrhage (Echogenic fluid) is a more specific finding, with an 86%-93% positive predictive value when hCG levels are abnormal and raises concern for a ruptured EP.

### Table 4: Incidence, risk factors and sonographic features of Non-tubal ectopic pregnancy Fig. 8 on page 19 Fig. 9 on page 19 Fig. 10 on page 20 Fig. 11 on page 20 Fig. 12 on page 21

<table>
<thead>
<tr>
<th>Site of EP</th>
<th>Incidence</th>
<th>Risk factors</th>
<th>US findings</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial pregnancy</td>
<td>2-4%</td>
<td>prior salpingectomy and in vitro fertilization</td>
<td>Eccentrically located gestational sac, surrounded by a thin myometrium (&lt;5 mm), interstitial line sign</td>
<td>higher mortality and morbidity because they can have later presentation and massive hemorrhage</td>
</tr>
<tr>
<td>Type</td>
<td>Frequency</td>
<td>Associated Conditions</td>
<td>Characteristics</td>
<td>Outcomes</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>--------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cornual pregnancy</td>
<td>&lt;1%</td>
<td>Mullerian anomalies</td>
<td>Implantation within the cornua of a bicornuate or a septate uterus. GS is surrounded by &lt; 5 mm of myometrium.</td>
<td>Rupture of a cornual pregnancy also results in catastrophic hemorrhage</td>
</tr>
<tr>
<td>Ovarian pregnancy</td>
<td>3%</td>
<td>Strong association with use of IUD</td>
<td>Gestational sac, chorionic villi, or an atypical cyst with a hyperechoic ring within the ovary, along with the normal fallopian tubes</td>
<td>Can manifest as part of a heterotopic pregnancy</td>
</tr>
<tr>
<td>Cervical pregnancy</td>
<td>&lt;1%</td>
<td>In vitro fertilization and a history of prior curettage</td>
<td>Hourglass or a figure eight shaped uterus, cardiac activity below the internal os</td>
<td>Sliding sign - Gentle transducer pressure do differentiate cervical EP and abortion in progress.</td>
</tr>
<tr>
<td>Caesarean Scar pregnancy</td>
<td>&lt;1%</td>
<td>Prior caesarean scar, multiple pregnancy</td>
<td>GS develops in the anterior part of the lower uterine segment and no myometrium is seen between the bladder wall and</td>
<td>Risk of uterine rupture with severe hemorrhage and hemodynamic collapse</td>
</tr>
<tr>
<td>Abdominal pregnancy</td>
<td>1.4%</td>
<td>Assisted reproduction</td>
<td>Absence of a normal intrauterine GS, GS located within the intraperitoneal cavity</td>
<td>Maternal mortality 7.7 times that of other locations of ectopic pregnancy</td>
</tr>
<tr>
<td>---------------------</td>
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<td>----------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Heterotopic pregnancy</td>
<td>1 in 30000 (1-3% among assisted reproduction)</td>
<td>Assisted reproduction</td>
<td>Simultaneous presence of an intrauterine and an extrauterine pregnancy</td>
<td>If persistent symptoms with abnormal beta-hCG after abortion of an IUP, heterotopic pregnancy should be suspected</td>
</tr>
</tbody>
</table>

**ROLE OF CT AND MRI** *Fig. 13 on page 22* *Fig. 9 on page 19* *Fig. 10 on page 20*

- Ultrasound is sufficient in most cases of EP.
- MRI is indicated in patients with (a) poor acoustic window and difficult transvaginal ultrasound (b) Strong clinical suspicion but inconclusive US.
- EP should be considered when hemoperitoneum or a pelvic mass is seen in a woman of childbearing age.
- CT is usually performed in the evaluation of abdominal or pelvic pain of unknown cause when pregnancy status is not known.
- Sonographic findings have MRI and CT correlates; cystic structure surrounded by a thick wall, hemoperitoneum, hematosalpinx, heterogeneous mass, tubal dilatation and wall enhancement can be found [12].
Table 5: Clinical and imaging features of major differentials for ectopic pregnancy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical clue</th>
<th>Sonography</th>
<th>Beta-hCG status</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early IUP</td>
<td>H/O amenorrhea and vaginal bleeding</td>
<td>No intrauterine GS or adnexal mass</td>
<td>Positive</td>
<td>Serial Beta-hCG - Normal doubling Follow-up US</td>
</tr>
<tr>
<td>Nonviable IUP</td>
<td>H/O amenorrhea and vaginal bleeding</td>
<td>Variable depending on the cause and stage.</td>
<td>Positive</td>
<td>Serial Beta-hCG- Decreasing, plateau or slow rise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Irregular contour of sac</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Decidual reaction &lt;2 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Choriodecidual reaction not echogenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Absent double decidual sac</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Low position</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupture corpus luteal cyst</td>
<td>2nd half of menstrual cycle and dominated by hemoperitoneum</td>
<td>Irregular thick walled cysts with heterogenous contents and hemoperitoneum</td>
<td>Negative</td>
<td>Laparotomy in unstable patients irrespective of EP or Rupture CL cyst</td>
</tr>
</tbody>
</table>
| **Ovarian torsion** | Abrupt onset | 1. Ovarian enlargement and edema  
2. enlarged peripheral follicles  
3. presence of ovarian mass  
4. abnormal ovarian position  
5. ipsilateral uterine deviation  
6. Cul de sac fluid  
7. absence of venous flow  
8. Twisted pedicle sign | Negative | MRI can be problem solving |
| **PID** | Cervical motion tenderness | 1. Thick walled fallopian tube with or without distension  
2. Tubo-ovarian/pelvic abscess  
3. Pelvic fat echogenicity  
4. Free fluid | Negative | CT/MRI for confirmation and to assess the extent of disease to decide on management |
<table>
<thead>
<tr>
<th>Appendixitis</th>
<th>Right upper quadrant or flank pain and tenderness in pregnancy due to gravid uterus</th>
<th>MRI - modality of choice if US equivocal</th>
<th>Negative</th>
<th>Most common surgical emergency in pregnancy</th>
</tr>
</thead>
</table>

**SUMMARY**

**Potential pitfalls**

1. 21% of EP demonstrate a #-hCG doubling time identical to that of intrauterine pregnancies (IUP)
2. Interstitial EP could be mistaken for cornual EP
3. Spontaneous abortion in progress mimics cervical EP
4. Visualization of IUP does not rule out EP- heterotopic pregnancy is possible albeit rare.
5. 'Ring of fire' sign is a nonspecific finding and may also be seen in a normal maturing follicle or a corpus luteal cyst.
6. Pelvic free fluid is seen in 50-75% of EP and does not necessarily imply tubal rupture. Non specific fluid is also detected in 20% of all IUP

**Pearls of EP diagnosis**

1. Absence of IUP does not imply EP. It should just trigger a detailed search for an ectopic pregnancy
2. IUP should be seen on Transvaginal US with #-hCG levels of > 2000 mIU/mL.
3. Differentiate true GS from pseudo gestational sac by looking for 'Double decidual sign'
4. Intrauterine findings of an EP include normal endometrium, pseudo gestational sac, trilaminar endometrium and thin-walled decidual cyst.
5. No single serum Beta-hCG level is diagnostic of an EP. Serial levels are necessary to differentiate between normal and abnormal pregnancies and to monitor resolution of EP once therapy has been initiated
6. If #-hCG levels increase by less than 50% during a 48-hour period, there is almost always a nonviable pregnancy either intra- or extra uterine.
7. An adnexal mass that is separate from the ovary is the most common finding of a tubal pregnancy seen in up to 89%-100% of patients.
Fig. 1: Gray scale USG showing normal intra uterine gestational sac (GS) with double decidual sign and fetal pole (arrow). E-endometrium, M- myometrium

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**Fig. 2:** Sonographic appearance of corpus luteum. (A) Dominant follicle. (B) Corpus luteal cyst with crenulated margins. (C) Corpus luteal cyst with irregular outline and heterogenous contents suggestive of hemorrhagic corpus luteal cyst.

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**Fig. 3:** Gray scale USG (A and B) showing complex solid right adnexal mass (arrow) separate from the ovary suspicious for ectopic pregnancy.

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**Fig. 4:** Doppler USG shows left adnexal GS with fetal pole and yolk sac (YS) separate from the left ovary (LTO) and uterus with peripheral vascularity suggestive of live left tubal EP.

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**Fig. 5:** Gray scale (A) and doppler USG (B) shows complex solid right adnexal mass (arrow) separate from the right ovary (asterisk) with peripheral ring of hypervascularity representing ‘Ring of fire’ sign suggestive tubal EP.

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Fig. 6: Uterine findings in EP. Gray scale USG (A) and (B) show oval cystic focus with single echogenic ring and thickened endometrium representing pseudo gestational sac. (C) Significant thickening of endometrial echo in known case of EP suggesting endometrial cast
**Fig. 7:** Gray scale USG (A and B) showing complex solid right adnexal mass (arrow) separate from the ovary with echogenic pelvic free fluid (asterisk) suggestive of tubal EP rupture with hemoperitoneum. Note made of intrauterine device (loop)

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**Fig. 8:** Ultrasound (A) of pelvis demonstrates gestational sac (yellow arrow) in left cornua with empty endometrial cavity (black arrow). Coronal T2 TSE (B) and post gadolinium (C) confirmed the cornual location of gestation sac

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**Fig. 9:** USG (A) and Sagittal T2W MRI (B) shows fetus with surrounding amniotic fluid in recto uterine pouch outside the uterus representing abdominal EP.

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**Fig. 10:** USG (A), axial and sagittal T2W MRI (Band C) shows GS with fetus in the uterine cervix (arrow) and associated endometrial thickening (U).

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Fig. 11: Gray scale USG (A) shows intrauterine GS. Gray scale (B) and doppler USG (C) shows complex right adnexal cystic mass (asterisk) separate from the right ovary (Arrow) suggestive of tubal EP. USG (D) shows echogenic fluid in the pelvis suggesting rupture of tubal EP.

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**Fig. 12:** USG (A and B), coronal (C) and axial (D) T2W MRI of the pelvis shows fetus in the left horn of bicornuate uterus (arrow). Right horn shows endometrial thickening (asterisk).

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Fig. 13: Axial non-contrast CT (A and B) shows high density ascites (asterisk) and complex solid right adnexal mass (arrow). Axial and coronal contrast CT (C and D) shows small enhancing focus (arrow) within the complex solid right adnexal mass suggestive of tubal EP rupture. Note made of IUD in uterus (U).

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Fig. 14: Axial (A) and coronal (B) contrast CT, doppler USG of right adnexa (C) and gray scale USG of left adnexa (D) shows bilateral complex tuboovarian abscess (arrows) with peripheral enhancement suggestive of complicated pelvic inflammatory disease.
**Fig. 15:** Gray scale USG of left ovary (A) shows normal appearance with follicles. Gray scale USG of right ovary (B) shows enlarged and edematous ovary with peripherally displaced follicles (arrow).

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**Fig. 16:** Doppler USG (A and B) of left adnexa shows normal vascularity of left ovary with low resistance waveforms. Gray scale and doppler USG (C and D) of right adnexa shows reduced vascularity of right ovary with absent diastolic flow suggesting ovarian torsion

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Conclusion

As ectopic pregnancy can have devastating outcomes, it is imperative for the radiologists to familiarize themselves with classic and atypical imaging features of tubal and non-tubal forms of ectopic pregnancy.
Personal information

Dr Subramaniyan Ramanathan MD
Fellowship in abdominal imaging (Ottawa, Canada)
Consultant Clinical imaging
Al Wakra Hospital

Hamad medical corporationTel: 4011 4509, P.O. Box: 82228, Doha-Qatar
References


