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## Urgent need to change clinical practices about postpartum contraception

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### Abstract

In the United States, maternal mortality and unintended pregnancy rates are increasing. There are growing disparities in maternal health between indigent, minority women and Caucasian women of higher socioeconomic status. Family planning has long been viewed as a solution to these problems. As reliance on permanent contraception has diminished, timely access to highly effective contraceptive methods, namely long acting reversible contraceptives, which includes the contraceptive hormonal implant and intrauterine device - has become even more important. For women in the United States and abroad, the time of delivery is the one reliable opportunity for women to receive medical care. Consistently, research has shown that providing contraception in the immediate postpartum period is safe, effective, feasible and cost effective. However, misperceptions, lack of supplies, and reimbursement issues combine to defeat attempts to provide the most effective methods of contraception during that hospitalization. We believe that it is time to tackle the problem of unintended and rapid repeat pregnancy using an evidence-based, patient-centered paradigm and to eradicate systemic barriers blocking access to contraceptive methods during hospital stay. This editorial will outline some of the more compelling evidence supporting this move and will provide insights from successful programs.

**Key words:** Postpartum contraception; Long acting reversible contraception; Subdermal contraceptive implant; Intrauterine device; Unintended pregnancy

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**Core tip:** The postpartum period is an ideal opportunity to initiate highly effective contraception, yet many women leave the hospital without any contraception. Provision of highly effective contraceptives, in parti-

cular long acting reversible contraceptives, such as intrauterine devices and contraceptive implants, is safe, desired, effective and cost saving. We review the need for immediate postpartum contraception and recommend changes within the medical system to facilitate this change.

Goldsmith C, Nelson AL. Urgent need to change clinical practices about postpartum contraception. *World J Obstet Gynecol* 2015; 4(3): 52-57 Available from: URL: <http://www.wjgnet.com/2218-6220/full/v4/i3/52.htm> DOI: <http://dx.doi.org/10.5317/wjog.v4.i3.52>

## INTRODUCTION

For the last three decades, the overall unintended pregnancy rate in the United States has been nearly constant at 50%. The 2014 estimate demonstrates that the overall rate has increased to 51%, but that greater disparities exist today than ever before. The rate of unintended pregnancy has declined to 34% among women of higher socioeconomic status (SES), but has increased to 62% among women of lower SES<sup>[1,2]</sup>. Unintended pregnancies can have severe health and economic consequences for both the mother and her fetus<sup>[3]</sup>. This is perhaps most notable among women with rapid repeat pregnancies (defined as a pregnancy 12-18 mo after delivery), which is linked to increased maternal and child morbidity and mortality<sup>[4-9]</sup>. Pregnancy rates within one year of delivery range from 6%-40% depending on the population studied, and are particularly high among adolescents<sup>[10-12]</sup>.

The provision of highly effective contraception in the postpartum period serves as a partial solution to the problem of unintended pregnancy and is uniquely able to drastically reduce rapid repeat pregnancy rates. Traditionally, the only contraception offered in the immediate postpartum period has been tubal ligation or progestin only pills. This is because it has been assumed that couples will remain abstinent for at least 6 wk, as instructed by the obstetrician. The more highly effective, reversible methods of contraception typically are not offered until the six week postpartum visit. The timing of this postpartum visit itself is anachronistic; it was designed to ensure the cervix and vagina had normalized so that the women could have a pap smear and a diaphragm fitting<sup>[13]</sup>. Unfortunately, clinging to this outdated standard creates barriers to accessing effective contraceptive methods and increases the risk for unintended pregnancy for several reasons. First, up to 35% of postpartum women (often the most vulnerable ones) do not return for postpartum care<sup>[11,12]</sup>. This is due often to changing insurance status. (In the United States, prenatal care, delivery and postpartum care up to 6 wk post-delivery are covered universally for low income citizens. For undocumented residents, however, only delivery care is covered generally). Among those

who do present, other barriers are often encountered, such as need to order long acting reversible contraceptives (LARC) devices (which necessitates yet another visit for placement) and lack of enthusiasm on the part of physicians. Surveys of practicing obstetrician/gynecologists and family physicians consistently show a lack of knowledge of LARC, specifically regarding intrauterine device (IUD) placement<sup>[14-17]</sup>. It is not surprising that only a fraction of those desiring LARC actually receive LARC at this visit<sup>[11,18]</sup>. Indeed, Potter found that while 25% of women desired LARC postpartum, only 12% actually were able to initiate LARC within 6 mo of delivery<sup>[18]</sup>. This disconnect mostly affects women of lower socioeconomic status and women who lost insurance coverage. Finally, even if women manage to present for postpartum care and are offered effective contraceptives, the visit may be too late for some women - as ovulation may return as early as 25 d postpartum for nonbreastfeeding women<sup>[19]</sup> and many couples do not observe the recommended 6 wk of abstinence postpartum<sup>[20,21]</sup>.

Provision of contraception in the immediate postpartum period has the potential to solve these problems. We hope to generate greater support for this practice by demonstrating the safety, effectiveness, patient satisfaction, and cost effectiveness of immediate initiation of top tier contraceptive methods.

## IMMEDIATE POSTPARTUM CONTRACEPTION IS SAFE

The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have provided clear guidance regarding the safety of immediate postpartum contraception. All progestin only methods are Category 1 (no contraindication) in nonbreastfeeding women and Category 2 (benefits outweigh risk) in breastfeeding women. Only combination methods containing estrogen are unsafe for at least 21 d postpartum due to associated risk for venous thromboembolic event (VTE)<sup>[22-24]</sup>. For women with known risk factors for VTE, initiation of combination hormonal methods should be delayed even longer until 42 d.

Frequently, breastfeeding women have been denied immediate postpartum hormonal contraceptive methods due to concerns about decreasing milk supply and/or passage of hormone into the breast-milk. Multiple studies have demonstrated that progestin only methods, including Depot Medroxyprogesterone Acetate (DMPA) and the etonogestrel implant do not delay lactogenesis<sup>[25]</sup>, impede milk production<sup>[26]</sup> or adversely impact overall breastfeeding continuation rates and success<sup>[20,27,28]</sup>. Moreover, infant growth and development is not affected by hormonal contraceptives, even when provided in the immediate postpartum period<sup>[25]</sup>. The levonorgestrel (LNG) IUD is less well studied. One small study suggests that



breastfeeding rates are lower among women receiving immediate postplacental LNG IUD compared to delayed insertion, though this was a secondary analysis of data designed to evaluate IUD continuation rates<sup>[12]</sup>. There are not data regarding infant growth and development with use of a LNG IUD placed immediately postplacental. However, given that the systemic dose of progestin is significantly lower with either DMPA or the etonogestrel implant, there is little basis for concern about any adverse impact the LNG IUD could have on infant growth and development.

The placement of intrauterine devices in the immediate postpartum period (within 10 min of placental expulsion) has been shown to be safe by many metrics. Immediate postplacental IUD placement has been researched in multiple settings internationally and with multiple types of IUDs, including Lippes Loops, Delta T, Delta Loop, Gyne T, CuT380A and LNG IUD<sup>[29-39]</sup>. These studies consistently show there is no increased risk of infection with immediate postplacental placement, though women diagnosed with chorioamnionitis, chlamydia or gonorrhea in pregnancy without evidence of a negative test of cure, or ruptured membranes for more than 24 h are not candidates for immediate postplacental IUD due to infection risk<sup>[23,34,37]</sup>. No increase in perforation rates has been reported when compared to interval insertion at 6-8 wk postdelivery<sup>[37]</sup>. Postpartum pain and bleeding also do not differ when comparing women receiving immediate postplacental IUDs and women receiving no contraceptive method<sup>[34]</sup>.

The risk of expulsion with postplacental IUD insertion is higher than seen with interval insertion at 6-8 wk postdelivery. The reported expulsion rate varies significantly in the literature, ranging from 0.3% to 24%<sup>[30,32-39]</sup>. This increased risk of expulsion appears to depend on mode of delivery and interval between placental delivery and IUD placement. Studies of IUDs placed immediately after a vaginal delivery show expulsion rates of 20%-24%<sup>[31,34,36]</sup>. When the IUD is placed at the time of a cesarean section, expulsion rates are typically lower (0.3%-5%) and similar to those seen with interval placement at 6 wk postpartum<sup>[29,34,36,40]</sup>. Additionally, placement that occurs greater than 10 min after delivery of the placenta is associated with higher rates of expulsion than placement less than 10 min after placental delivery<sup>[31,41,42]</sup>. These findings appear consistent across multiple types of IUDs, indicating that the question of which IUD to place should be made based on patient preference and IUD availability. While the risk of expulsion may be higher with immediate postplacental IUD insertion, this risk must be weighed against the patient's risk of not returning for interval insertion. For many women with minimal access to care, the expulsion risk is worth taking. While specialized training is needed to place IUDs in the immediate postpartum setting, short didactic sessions with residents have demonstrated excellent outcomes<sup>[43]</sup>.

The placement of contraceptive implants in the postpartum period is more straightforward. The implant

can be inserted at any time during the hospital stay. The insertion technique and associated risks with placement in the immediate postpartum period are no different than those associated with interval placement.

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## PROVISION OF IMMEDIATE POSTPARTUM CONTRACEPTIVES PREVENT RAPID REPEAT PREGNANCY

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Multiple studies demonstrate that contraceptive continuation rate at 6 mo and at one year post-delivery are higher among women who received LARC in the immediate postpartum period than in women who receive delayed LARC placement at the six week postpartum visit<sup>[29,35,37,44,45]</sup>. More impressive is the data demonstrating that provision of immediate postpartum contraceptive implants decreased repeat pregnancy rates at one year postpartum, despite the fact that 14% had discontinued the implant at 12 mo postpartum<sup>[10]</sup>. When evaluating women who wanted permanent contraception in the immediate postpartum period, women who did not undergo a tubal ligation had higher rates of pregnancy when compared to women who did not desire permanent sterilization postpartum despite both groups having similarly low attendance at the postpartum visit<sup>[46]</sup>.

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## WOMEN ARE SATISFIED WHEN PROVIDED IMMEDIATE POSTPARTUM CONTRACEPTION

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Women who receive immediate postpartum contraception are as satisfied or more satisfied with their methods than women undergoing delayed insertion<sup>[29,39]</sup>. When using the continued use of contraceptive method as a marker for patient satisfaction, we likewise find that more than 80% women receiving immediate postpartum LARC continue using it a year after placement<sup>[35,37,44,45]</sup>. This is significantly higher than the approximately 50% continuation rate for combination oral contraceptive pills<sup>[47]</sup>. Less is known about the continuation rates of DMPA when provided in the immediate postpartum period. Finally, contraceptive side effects occur at equal rates when comparing immediate and delayed postpartum contraception initiation<sup>[48]</sup>.

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## IMMEDIATE POSTPARTUM CONTRACEPTION IS COST EFFECTIVE

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Provision of contraception has consistently been shown to be cost effective. Recently, two separate studies have found that immediate postpartum contraception is not only cost effective, but it is cost saving. Han *et al.*<sup>[49]</sup> found that every dollar spent to provide immediate postpartum etonogestrel implants to adolescents saved \$6.50 within two years post-delivery. These findings factored in a high discontinuation rate (14%)

among those receiving the implant in the immediate postpartum period and still noted cost savings by providing immediate postpartum implants. Washington *et al.*<sup>[50]</sup> looked at immediate postplacental IUD placement and found a cost savings of \$282540 per 1000 women over 2 years. Perhaps more interestingly, these cost savings persist even if the expulsion rate of immediate postplacental IUDs is inflated to 38%.

## WHY THE DELAY?

The medical evidence regarding health, safety, cost and patient satisfaction supports the use of immediate postpartum contraception. Yet, several barriers prevent the wide adoption of immediate postpartum contraception. In many locations, access to contraceptives and access to healthcare providers trained to provide contraceptives limits the ability to provide this service. Additionally, as many hospitals are owned by religiously affiliated organizations, there are more restrictions placed on what contraceptives, if any, may be provided to women. From an ethical perspective, every woman considering her delivery hospital options should be informed during her prenatal care of any deliberate institutional policies that would prohibit her access to postpartum contraception. Failure to do so is equivalent to sending a trauma victim to a hospital without emergency services. Regarding permanent contraception, women receiving state or federally funded health coverage must sign consents for the procedure at least 30 d in advance. Again, this presents a great challenge for women lacking access to routine health care as it requires not only that the patient have initiated prenatal care early in pregnancy, but also that her provider discussed contraception, including sterilization, in a timely manner. Additionally, the delivering provider must have a copy of this consent at the time of delivery in order to provide sterilization. Finally, the surgical staff must be available and willing to provide the procedure. These logistical challenges reduce the chances a woman will obtain a tubal ligation. Research shows only 54% of women requesting postpartum tubal ligation obtain the procedure. Of those that did not undergo tubal ligation, 37% identified problems with informed consent paperwork as the reason<sup>[51,52]</sup>. Perhaps the greatest barrier to the provision of immediate postpartum contraception is the lack of reliable hospital reimbursement. Most insurance companies in the United States reimburse for prenatal care, delivery and postpartum care as a global package. This ensures that, while tubal ligations are covered by insurance during the inpatient stay, any LARC device placed during hospitalization is not covered by insurance companies. Indeed, only placement in the outpatient setting during the postpartum visit is reimbursable.

Change within the healthcare system is difficult and slow, but it is possible. Two barriers in particular seem ripe for transformation. First, medical providers are being better educated about both the safety of immediate

postpartum contraception and the actual technique of providing postplacental IUDs. Contraceptive implants require only that the provider undergo a brief 2-3 h training course for certification. As referenced above, surveys demonstrate there is still a lack of knowledge among providers and their staff regarding LARC, but there has been improvement. More recent graduates generally are more knowledgeable about immediate postpartum contraception and LARC. Clinicians will need to remember to include counseling on contraception, including sterilization, during prenatal visits so that a plan can be in place for each patient at the time of delivery. Second, the payment scheme for delivery needs to be altered to allow hospitals to be reimbursed for immediate postpartum contraception. This has been accomplished in eleven states in the United States by creating a separate Medicaid billing code for immediate postpartum contraception coverage.

## CONCLUSION

The evidence clearly demonstrates the need for improving the provision of immediate postpartum contraception, given its safety, high continuation rates, low failure rates and high satisfaction. Most importantly, providers need to be vocal advocates. We need to advocate for what is right for the patient and eliminate outdated practices that are clearly inferior. We need to press for immediate postpartum contraceptive coverage by all third party payors in all states so that women can receive the best care regardless of where they live and what insurance they have.

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## Avoiding misdiagnosing an early intrauterine pregnancy as an ectopic pregnancy

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### Abstract

In women at risk for an ectopic pregnancy, every effort should be made to exclude the presence of an intrauterine pregnancy before embarking on an irreversible treatment for ectopic pregnancy. The diagnosis of ectopic pregnancy, unless directly visualized with transvaginal ultrasound, is made with the exclusion

of an intrauterine pregnancy. Measurement of human chorionic gonadotrophin and progesterone levels, and transvaginal ultrasound are the tools used to evaluate early pregnancy. In women at risk for an ectopic pregnancy, every effort should be made to exclude the presence of an intrauterine pregnancy before embarking on an irreversible treatment course. Methotrexate is an antimetabolite that inhibits DNA synthesis and repair and cell replication. It is administered to ostensible destroy a pregnancy, especially ectopic pregnancies. When administered to an intrauterine pregnancy, embryonic death and missed abortion is the most common result, but early embryos that survive this exposure are likely to have multiple anomalies. The mistaken administration of methotrexate to an intrauterine pregnancy is made because of misinterpretation of the discriminatory zone of human chorionic gonadotropin (hCG), misinterpretation of early hCG serum levels, misinterpretation of early transvaginal ultrasound images, and failure to clinically correlate hCG levels and ultrasound findings.

**Key words:** Ectopic pregnancy; Ultrasound; Human chorionic gonadotropin; Methotrexate

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**Core tip:** In women at risk for an ectopic pregnancy, every effort should be made to exclude the presence of an intrauterine pregnancy before embarking on an irreversible treatment course. Methotrexate is an antimetabolite that inhibits DNA synthesis and repair and cell replication. It is administered to ostensible destroy a pregnancy, especially ectopic pregnancies. When administered to an intrauterine pregnancy, embryonic death and missed abortion is the most common result, but early embryos that survive this exposure are likely to have multiple anomalies.

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## INTRODUCTION

In women at risk for an ectopic pregnancy, every effort should be made to exclude the presence of an intrauterine pregnancy before embarking on an irreversible treatment for ectopic pregnancy, such as the administration of methotrexate. When methotrexate is administered to an intrauterine pregnancy, embryonic death with missed abortion is the most common result, but case reports of methotrexate embryopathy have described embryos that have survived early methotrexate exposure.

## LITERATURE RESERACH

This is a clinical perspective from experience with cases when methotrexate has been mistakenly administered to an undiagnosed intrauterine pregnancy. Included is a review of serum hCG and progesterone levels and ultrasound interpretation.

### Clinical characteristics

The diagnosis of ectopic pregnancy, unless directly visualized with transvaginal ultrasound, is made with the exclusion of an intrauterine pregnancy. The confirmation of an intrauterine pregnancy with transvaginal ultrasound relies upon recognition, initially of a true gestational sac, followed soon thereafter, by recognition of structures within the sac consistent with a developing embryo. The term "gestational sac" is a sonographic term and not an anatomical structure. A true gestational sac has a thick echogenic rim, a trophoblastic decidual reaction, surrounding a sonolucent center, the chorionic sac<sup>[1]</sup>. The intradecidual sign is the presence of such a sac buried beneath the surface of the endometrium, appearing eccentrically positioned within the endometrium (Figure 1). A "pseudosac" is a collection of fluid within the endometrial cavity itself, created by bleeding from the decidualized endometrium associated with an extrauterine pregnancy implantation (Figure 2). The precise location of such an early sonolucent uterine fluid collection should distinguish between a true gestational sac and a pseudosac.

Prior to the recognition on a definite intrauterine pregnancy, transvaginal ultrasound measurement of the endometrial echo thickness in early gestation can be helpful in predicting pregnancy location. Spandorfer *et al*<sup>[2]</sup> reporting on 117 pregnancies with a gestational age between 5.3 and 6.3 wk found statistically different endometrial echo thicknesses between patients who eventually had normal intrauterine, failed intrauterine, and ectopic gestations. Patients with normal pregnancies had endometrial echo thicknesses of  $13.42 \pm$

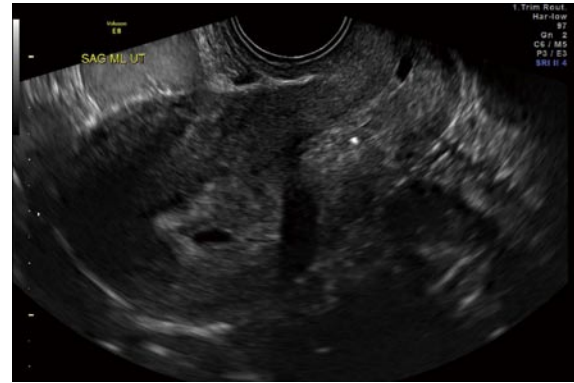


Figure 1 Transvaginal ultrasound image of a gestational sac consistent with an early intrauterine pregnancy.

0.68 mm. In contrast, those with failed intrauterine and ectopic gestations measured  $9.28 \pm 0.88$  mm and  $5.95 \pm 0.35$  mm, respectively ( $P < 0.01$ ). In this report, 97% of patients with an echo no greater than 8 mm had abnormal pregnancies, and 71% of these abnormal pregnancies were ectopic in location. Only 41% of those patients with an echo thickness greater than 8 mm were abnormal, and only 14.7% were ectopic in location. No patient with an endometrial echo thickness greater than 13 mm had an ectopic pregnancy, and no patients with an echo thickness less than 6 mm had a normal pregnancy. Other authors have not been able to duplicate these discrete, well-stratified echo thickness separations<sup>[3-5]</sup>. Therefore, such absolute endometrial thickness numbers cannot be absolutely relied upon, but attention to endometrial thickness can be helpful in predicting pregnancy location, especially when the endometrial thickness is very thin or very thick.

The "discriminatory zone" of human chorionic gonadotrophin (hCG) is that level of serum hCG at which a normal and singleton gestation can be visualized within the endometrial cavity with transvaginal ultrasound. Depending upon the lab and the reference standard used, that hCG level is 1500 to 2000 mIU/mL. A failing pregnancy, including an ectopic implantation, should be considered, but is not confirmed, when this hCG threshold is reached and an intrauterine gestational sac is not seen with transvaginal ultrasound<sup>[6]</sup>.

The possibility of ectopic pregnancy is frequently considered before hCG has reached the discriminatory zone and before ultrasound recognition<sup>[7]</sup>. Human chorionic gonadotropin rises exponentially in early normal pregnancy and should rise at least by 53% in 48 h<sup>[8]</sup>. This exponential rise is less reliable after 10000 mIU/mL, and at this level pregnancy is better evaluated with ultrasound. Fifteen percent of normal intrauterine pregnancies can demonstrate an abnormal early rise of hCG, but for the majority of gestations, when the hCG rise is abnormal, at a plateau, or falling, an abnormal pregnancy is confirmed, but not its location<sup>[9]</sup>.

When exact pregnancy dating is available, an intrauterine pregnancy, regardless of embryonic number,



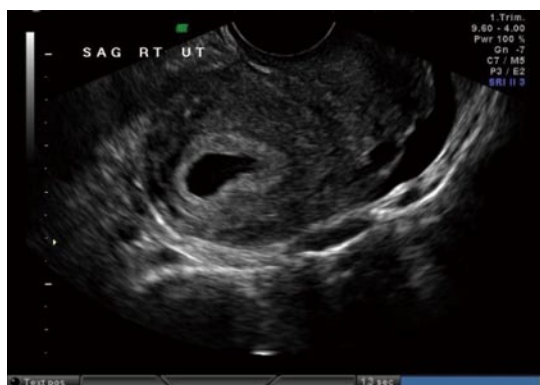


Figure 2 Transvaginal ultrasound image of a fluid collection within the endometrial cavity, a pseudosac, consistent with an extrauterine pregnancy.



Figure 3 Transvaginal ultrasound image of an intrauterine true gestational sac containing a yolk sac.

should be identified within the endometrial cavity with transvaginal ultrasonography by 24 embryonic days, or 38 menstrual days (exact 28 d menstrual cycle)<sup>[10]</sup>. This exact pregnancy dating does not rely on human chorionic gonadotropin levels. Therefore, failure to identify an intrauterine pregnancy with such exact dating is presumptive evidence of a failing pregnancy, which could be ectopic in location. Without such exact pregnancy dating, and with no intrauterine pregnancy identified with transvaginal sonography: the “non-diagnostic ultrasound”, a serum level of hCG is needed for ultrasound interpretation<sup>[10]</sup>.

Usually, the transvaginal ultrasound identification of an intrauterine pregnancy reliably excludes an extrauterine implantation. A yolk sac is the first visible structure within the gestational sac, and is a distinct circular structure with a bright echogenic rim and sonolucent center (Figure 3), and is recognized 3 wk post-conception (5 wk after the last menstrual period). The embryo is first recognized as a thickening along an edge of the yolk sac, and embryonic cardiac motion can be first observed 3 1/2 to 4 wk post-conception (5 1/2-6 wk after last menstrual period).

An exception to the above is the presence of a heterotopic pregnancy: the co-existence of an extrauterine implantation with an intrauterine pregnancy. Traditionally, the incidence of heterotopic pregnancy in spontaneous cycles has been reported to be 1 in 30000 pregnancies<sup>[11]</sup>. However, its incidence is actually 1 in 3889 pregnancies<sup>[12]</sup>. The incidence is even higher (1 in 100 pregnancies) in women conceiving with *in vitro* fertilization and embryo transfer<sup>[13]</sup>. Should a clinical presentation or abnormal pelvic ultrasound appearance suggest an ectopic pregnancy, despite visualization of an intrauterine gestation, the diagnosis of heterotopic pregnancy should be considered, with the probable need for diagnostic laparoscopy confirmation and treatment.

A serum progesterone level can be helpful when the hCG is elevated, the endometrial echo is thickened and no gestational sac is seen. In a study spanning several years and yielding 3674 consecutive emergency room pregnant women visits, a serum progesterone level

less than 5 ng/mL had a specificity of nearly 100% in detecting a failing pregnancy<sup>[14,15]</sup>. Therefore, with this low progesterone level, uterine curettage can be used to differentiate between a failing intrauterine pregnancy and an ectopic without the fear of interrupting a normal intrauterine pregnancy. When chorionic villi are seen on pathology, the diagnosis is a failed intrauterine pregnancy. If no chorionic villi are retrieved from the uterus, the pregnancy is somewhere else. An exception to this would be with a history of heavy vaginal bleeding consistent with a completed spontaneous pregnancy loss. Therefore, after uterine evacuation and absent chorionic villi, hCG should be re-measured. A falling hCG level would support the diagnosis of a spontaneous loss, and continued observation is recommended. With a post uterine evacuation persistently elevated hCG, ectopic pregnancy is confirmed.

Methotrexate is an antimetabolite that binds to the catalytic site of dihydrofolate reductase, interrupting the synthesis of purine nucleotides and the amino acids serine and methionine, thus inhibiting DNA synthesis and repair and cell replication. It affects actively proliferating tissues such as bone marrow, buccal and intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue. Systemic methotrexate has been used to treat gestational trophoblastic disease since 1956 and was first used to treat ectopic pregnancy in 1982<sup>[16]</sup>. It is administered to ostensibly destroy a pregnancy, especially ectopic pregnancies. When administered to an intrauterine pregnancy, embryonic death and missed abortion is the most common result, but case reports of methotrexate embryopathy have described embryos that have survived early methotrexate exposure<sup>[17-23]</sup>. The gestational age at exposure to methotrexate is critical for the type of malformations observed<sup>[17-23]</sup>. In particular, exposure at 5 to 6 wk gestation, which is often the case in misdiagnoses of ectopic pregnancy, may lead to methotrexate embryopathy, including musculoskeletal, conotruncal, cardiac and central nervous system abnormalities<sup>[17-23]</sup>. Cardiac defects include Tetralogy of Fallot, perimembranous ventricular septal defect, patent foramen ovale, and increased pulmonary artery pressures. Intrauterine growth restriction occurs,



Figure 4 Transvaginal ultrasound image of a thickened endometrial echo before identification of what will be an intrauterine pregnancy.

and, after delivery, neurodevelopmental delay is common.

Administration of methotrexate to a woman with a presumptive diagnosis of ectopic pregnancy, which eventually turns out to have an intrauterine pregnancy, results from the following:

#### **Misinterpretation of the discriminatory zone of hCG**

As stated, the discriminatory level of hCG is defined by a "normal and singleton" gestation, *i.e.*, a single embryo pregnancy that is living and intrauterine. If a pregnancy is not seen within the endometrial cavity with transvaginal ultrasound when the hCG level has reached the discriminatory zone, an ectopic pregnancy may be suspected, but is not diagnosed with certainty. A single early hCG level is only a marker for gestational age, and clinical parameters are more important in the decision-making process. An early multiple gestation may not be seen when the singleton hCG discriminatory level has been reached, and this should especially be considered in those women who have conceived with assisted reproduction. Also, because an abnormal pregnancy would be expected to have a lower hCG level at any given gestational age, delaying the performance of a vaginal ultrasound until the hCG level has reached the discriminatory level could miss the early opportunity to diagnose an ectopic pregnancy.

Because of the variation in vaginal ultrasound technical and interpretive abilities and laboratory hCG levels, before embarking on treatment for a presumed ectopic pregnancy, especially with methotrexate, every pregnancy should be given the benefit of the doubt, even if undesired. The diagnosis may require the use of diagnostic laparoscopy for confirmation or, simply, more time and serial measurements of hCG and serial ultrasounds until the diagnosis is certain.

#### **Misinterpretation of early hCG serum levels**

Barnhart, et al, have redefined early hCG curves<sup>[8]</sup>. They report a cohort of women who presented with abdominal pain and/or vaginal bleeding, symptoms which would place these women at risk for ectopic implantation, but who eventually had normal intrauterine pregnancies.

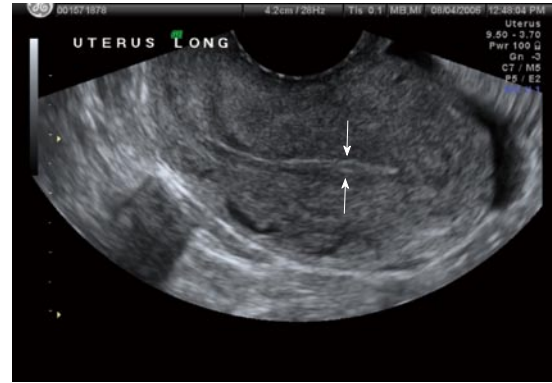


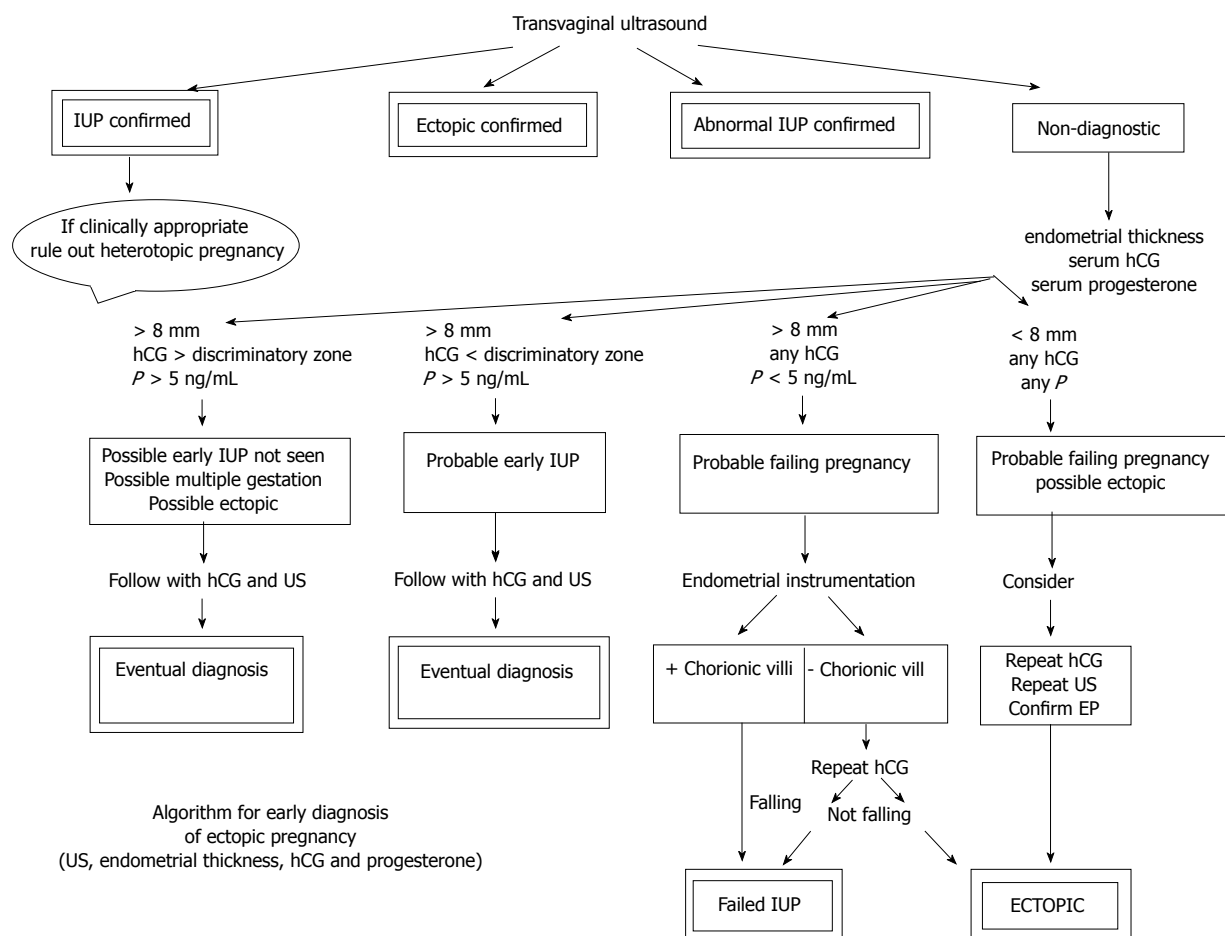
Figure 5 Transvaginal ultrasound image of a thin endometrial echo associated with and ectopic pregnancy.

Ninety-nine percent of these early normal intrauterine pregnancies demonstrated an early hCG rise of at least 53% in 48 h. Relying on hCG measurements less than after a true 48 h interval or the use of the old concept of true doubling or a 66% rise in 48 h could misdiagnose an intrauterine pregnancy as an ectopic<sup>[10]</sup>.

#### **Misinterpretation of early transvaginal ultrasound findings**

In a woman with a positive pregnancy and before the recognition of an intrauterine pregnancy with transvaginal ultrasound, endometrial echo thickness can be evaluated (Figures 4 and 5). As stated before, endometrial echo thickness can be helpful, but not definitive, in diagnosing pregnancy location: the thinner the endometrial echo, especially when less than 8 mm, the more likely the gestation is an ectopic implantation<sup>[2]</sup>. As stated before, absence of an intrauterine gestational sac on transvaginal ultrasound is not diagnostic of an extrauterine implantation, and clinical parameters must be considered in addition to absolute hCG levels, and because of the variation in the technical quality and interpretive ability of vaginal ultrasound and variation in laboratory hCG levels, the diagnoses of an ectopic pregnancy should not be made based on a single non-diagnostic ultrasound or a single hCG level. Furthermore, the location and appearance of an early intrauterine fluid collection may not always meet the criteria for a true gestational sac: eccentrically located sonolucent area surrounded by an echogenic rim.

Emergency room bedside sonography performed by emergency room personnel may differ significantly in quality and protocol from sonography performed by radiologists or trained gynecologists. A recent emergency room study reported that within a group of 161 women who were eventually proven to have a living intrauterine pregnancy, 47 (29%) were missed with initial emergency room bedside sonography with hCG levels as high as 100000 mIU/mL (mean hCG level of missed intrauterine pregnancies was 6633 mIU/mL)<sup>[21]</sup>. When the transvaginal ultrasound imaging interpretation is rendered by an emergency room physician or a radiologist, it would be prudent for the



**Figure 6** Non-surgical algorithm for the early diagnosis of ectopic pregnancy utilizing vaginal ultrasound, including endometrial echo thickness, serum human chorionic gonadotropin and serum progesterone. hCG: Human chorionic gonadotropin; US: Ultrasound; EP: Ectopic pregnancy; IUP: Inverted urothelial papilloma.

treating gynecologist to view the ultrasound images and discuss the findings with the other physician before embarking of treatment of a suspected ectopic pregnancy. Unless absolutely diagnostic, caution is recommended in interpreting a single hCG level and a single ultrasound image.

## CONCLUSION

The true overall incidence of methotrexate exposure to early intrauterine pregnancies is unknown and probably under reported because few cases are found in the medical literature. Every effort should be made to exclude an intrauterine pregnancy before embarking on an irreversible ectopic pregnancy treatment course, *i.e.*, methotrexate. Unless a clinical emergency exists, which would also be a contraindication to medical management, expectant management with follow up hCG levels and follow up ultrasound imaging will eventually lead to the correct diagnosis. Administration of methotrexate is never an emergency. Laparoscopy confirmation should not be disregarded when felt clinically appropriate. A thickened endometrial echo without a gestation sac needs follow up ultrasound imaging. Any intrauterine fluid collection should be

considered a probable gestational sac until proven otherwise. A low serum progesterone can justify endometrial curettage to differentiate between a failing intrauterine pregnancy and an ectopic pregnancy. The rise of hCG should be interpreted in view of the new hCG curves.

Figure 6 is a suggested non-surgical diagnostic algorithm utilizing these diagnostic principles. The algorithm has not been tested to yield sensitivity, specificity, positive or negative predictive values, but adds the evaluation of endometrial thickness to the criteria of previous non-surgical algorithms. Every woman with the potential diagnosis of ectopic pregnancy should be counseled on the need for close follow up while awaiting diagnostic confirmation, rather than proceeding with an irreversible treatment with only a suspicion.

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## Value of neoadjuvant chemotherapy in advanced ovarian cancer

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(NACT) are not definitive. Several randomized trials and meta-analyses demonstrate that this chemotherapy regimen decreases the morbidity and mortality rates and increases complete cytoreduction rates. If combined with hyperthermic intraperitoneal chemotherapy (HIPEC), NACT could potentially further improve upon these already promising results. Moreover the use of NACT could help in evaluating the chemo-sensitivity of the cancer, thus preventing unnecessary HIPEC procedures in chemo-resistant patients. NACT should definitely be considered as a preferred regimen in the management of advanced ovarian cancer, especially in association with cytoreductive surgery + HIPEC procedure in the context of a multidisciplinary team management in an experienced cancer centre.

**Key words:** Epithelial ovarian cancer; Neoadjuvant; Chemotherapy; Hyperthermic intraperitoneal chemotherapy; Treatment; Oncology; Cytoreductive surgery

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**Core tip:** Data about the use of neoadjuvant chemotherapy in advanced ovarian cancer are not sufficient to support its extensive application. However encouraging results came from the existing studies. Future well designed studies are needed to clarify some aspects of this chemotherapy regimen and its association with the other form of pharmacological and surgical therapy.

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### Abstract

Data regarding the role of neoadjuvant chemotherapy

### INTRODUCTION

One of the most common malignancies and one of

the principal causes of death among gynaecological neoplasm is epithelial ovarian cancer (EOC)<sup>[1]</sup>. The majority of EOC patients (about 70%) present with an advanced FIGO (International Federation of Gynecology and Obstetrics) stage disease (III or IV)<sup>[2-5]</sup>. Currently the standard treatment for these patients consists of complete cytoreduction (CC) followed by combined systemic chemotherapy of a platinum agent and paclitaxel<sup>[1,6]</sup>. Optimal cytoreduction was found to be one of the strongest survival determinants among patients with advanced stage<sup>[7-12]</sup>.

## NACT AND INTERVAL DEBULKING SURGERY

Recently, interval-debulking-surgery (IDS) after a short course of neoadjuvant chemotherapy (NACT), usually three cycles, has been demonstrated to be a viable alternative in those patients with low probability to obtain a CC during primary debulking surgery (PDS)<sup>[13]</sup>. Three randomized controlled trials (RCT) have demonstrated that overall survival (OS) and progression-free survival (PFS) in patients who received NACT plus IDS were not different from patients who received PDS. However, patients who received NACT had significantly lower adverse events and lower mortality after IDS than after PDS<sup>[14-16]</sup>.

The first RCT, by the European Organization for the Research and Treatment of Cancer (EORTC) evaluated the benefit of IDS after suboptimal PDS. One-hundred and forty patients treated with three cycles of cisplatin and cyclophosphamide chemotherapy followed by IDS plus three cycles of ACT were compared with 138 similar patients receiving the same chemotherapy regimen without IDS. Data obtained from this study showed that patients from the IDS group had a median survival time statistically significant longer (26 mo) than patients not treated with IDS (20 mo)<sup>[14]</sup>.

The second RCT conducted by the Gynecologic Oncology Group, evaluated 550 patients (stage III-IV) with a residual disease > 1 cm after PDS<sup>[15]</sup>. All patients received three cycles of initial chemotherapy with cisplatin and paclitaxel followed by response evaluation. Patients with no disease progression were randomized to IDS plus three additional cycles of ACT or additional chemotherapy alone. No differences between the two groups were found with regard to PFS or OS<sup>[15]</sup>.

The third RCT performed by EORTC with the National Cancer Institute of Canada (NCIC) compared PDS with NACT plus IDS<sup>[16]</sup>. Seven hundreds and eighteen patients with EOC, fallopian tube or primary peritoneal carcinoma were included. All patients had stage IIIC-IV disease and were randomized to PDS plus platinum chemotherapy or NACT plus IDS. The CC was optimal (residual disease ≤ 1 cm) in 41.6% of patients after PDS and in 80.6% after IDS. PFS and OS were similar in both groups. Postoperative complications and postoperative mortality were higher after PDS<sup>[16]</sup>.

A meta-analysis from Bristow *et al.*<sup>[17]</sup> showed poor

results for NACT used instead of PDS in advanced EOC. However this meta-analysis also demonstrated increased survival with an easier IDS prior to NACT and decreased survival with increasing number of chemotherapy cycles prior to IDS. Chua *et al.*<sup>[18]</sup> suggested that the treatment of advanced EOC should primarily involve a massive surgical effort for CC, and NACT may be considered when the extent of the disease decreases the possibility of achieving a CC<sup>[1]</sup>. Another meta-analysis by Kang and Nam<sup>[19]</sup> showed a positive correlation between use of NACT and increased rate of CC in patients at high risk for suboptimal debulking and/or unfavourable general conditions.

Tangjitgamol *et al.*<sup>[20]</sup> stated in a third meta-analysis that no conclusive evidence could be obtained to determine whether NACT increased or decreased survival rate.

## NACT AND CRS PLUS HIPEC

Extensive data from the last ten years demonstrate that improved long-term results can be achieved in select patients using cytoreductive surgery (CRS), including parietal and visceral peritonectomy procedures, in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC)<sup>[18,21-30]</sup>.

Data from the literature are encouraging though not entirely homogeneous<sup>[31]</sup>. Nevertheless, as stated by Markman<sup>[32]</sup>, the absence of phase-III trials suggests a few considerations before definitively validating CRS plus HIPEC as a viable strategy for first-line treatment of advanced EOC<sup>[1]</sup>.

While the majority of patients with EOC (up to 80%) respond to the first-line platinum based chemotherapy, almost 20% of patients are resistant or refractory<sup>[1,33]</sup>. The greatest risk is for patients requiring CRS plus HIPEC<sup>[1]</sup>. CC is associated with high postoperative morbidity and mortality rates especially in advanced cases<sup>[9,34,35]</sup>. This could potentially be increased by HIPEC as it remains a burdensome procedure. For this reason, the goal would be to select patients suitable to achieve the maximum benefit and to reduce the need for surgical resections<sup>[1]</sup>. Even if NACT followed by CRS plus HIPEC does not show better results in terms of PFS and OS<sup>[16,36]</sup>, the evaluation of the NACT response may help in selecting for HIPEC-only patients who demonstrate chemo-sensitivity. In fact, NACT could have the additional benefit of providing the “*ex-juvantibus*” chemo-sensitivity determination<sup>[1]</sup>. HIPEC with platinum compounds and taxanes in fact has been demonstrated as feasible and safe<sup>[30,37]</sup>.

The addition of NACT to the current treatment regimen as documented in the literature provides some advantages with regards to morbidity reduction and completeness of cytoreduction, especially in preoperatively well-staged patients. As CC is one of the strongest predictors of survival, it is not yet well-understood why studies have failed to show an improvement in OS or DFS with NACT<sup>[7]</sup>. Nevertheless,



NACT shows great promise in its potential to prevent unnecessary use of HIPEC and to reduce surgical load, thus decreasing post-operative morbidity and mortality.

## CONCLUSION

The use of NACT in the treatment of advanced EOC is progressively increasing. Studies about its use in several setting are on-going. This chemotherapy regimen should be considered as a preferred regimen in the management of advanced EOC, especially when combined with CRS plus HIPEC procedure in the context of a multidisciplinary team management in an experienced cancer centre. Results from the on-going RCT will clarify several issues about the association and the real survival effects of NACT associated to CRS plus HIPEC. Future well-designed studies are needed to clarify some aspects of this chemotherapy regimen and its association with the other form of pharmacological and surgical therapy.

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## Single incision slings: Past, present, and future

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### Abstract

Pubovaginal slings have become the gold standard to treat stress urinary incontinence. Traditionally, the sling referred to a suspensory that was placed under the urethra and brought through the retropubic space and anchored on either side of the midline. Since this original concept, there have been many materials used for the

sling, and there have been many different anchoring approaches. Most agree that one of the best materials is polypropylene mesh. However, the means of anchoring the device and where best to have this anchorage placed is debatable. The options for anchoring simply include using darts *vs* not to hold the sling in place. The location of this anchorage, on the other hand, is much more controversial. The main locations are retropubic, transobturator, and *via* a single incision. The obturator and retropubic slings have become the standard of care over time. The single incision sling, on the other hand, is starting to be more acceptable which has resulted in it being used more frequently. The single incision relies on mainly anchoring the sling through the obturator internus muscle with possible inclusion of the obturator membrane. The purpose of this review article is to present the data that exists for the use of the single incision sling.

**Key words:** Sling; Stress urinary incontinence; Incontinence; Single incision sling; Surgery

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**Core tip:** Polypropylene slings have become the mainstay of therapy for treating stress urinary incontinence in women. Historically, these slings have worked well, but there was always the concern of morbidity. The goal of the single incision sling (SIS) is to provide high efficacy with minimal side effects. The initial use of the SIS was mottled by confusion with the techniques for deployment. The most recent data has shown that when the SIS is used appropriately the success rates are similar to standard mid-urethral slings with minimal risk of bladder, vascular, or nerve injury as well as chronic pain.

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## INTRODUCTION

Pubovaginal slings have been used for decades. However, it wasn't until the mid to late 1990's that the use expanded. This expansion was due in part to the use of polypropylene mesh. It was Ulmsten *et al*<sup>[1]</sup> who proved to the medical community that one could correct stress urinary incontinence (SUI) by using a piece of polypropylene mesh. Additionally, at the same time the synthetic sling became available, there was an enormous push by the device companies to educate the physicians. This education did not only include Urologists who were the main surgeon providing slings to their patients but it included gynecologists. This initially involved using transvaginal tape through the retropubic space. Although this worked well, there still was the potential for adverse events involving the bowel, bladder, and vascular structures<sup>[2,3]</sup>. Most of these complications were due to the use of trocars in the retropubic space. The transobturator sling was an evolutionary advancement, which attempted to preserve the high success rates of retropubic polypropylene slings while minimizing the chance of surgical complications. This sling in theory eliminated the chance of bowel injury and significantly reduced the chance of bladder injury. However, it still proved to possibly cause vascular injury to the obturator vessels or nerve injury to the obturator nerve. These patients were also at risk of groin pain either from muscular or tendon injury or perhaps neurologic irritation. Also, the medical community was looking for a sling that was the least invasive with high success rates and minimal chance of complications. In response to these desires, a polypropylene sling using a single vaginal incision was created.

The single incision sling (SIS) technique enables the user to place a piece of polypropylene mesh through a single vaginal incision. The idea of a SIS was first used approximately 7 years ago. The sling material varied in lengths from 8-9 cm. Some of these slings used fixation anchors while others relied more on scaring to provide fixation. Throughout the years, there were even variable length slings developed. The techniques for placement of many of the previous SISs were not consistently uniform. As a result, the early data for the SISs were not always comparable to those seen with transobturator and retropubic slings. However, the most recent retrospective and prospective studies on the use of second-generation SIS systems have demonstrated relatively high success rates with minimal morbidity. This review will provide evidence in support of the SIS.

## SURGICAL TECHNIQUE

To enhance the understanding of the SIS, it is important to understand how it is placed. The description below provides the generalized technique for the placement of the SIS.

Prior to the surgery, IV antibiotics are administered.

The patient is then given either local, general, or regional anesthesia at the discretion of the surgeon in combination with the anesthesiologist. A dorsal lithotomy position is then achieved to facilitate surgery. A foley is inserted to empty the bladder. A 1-2 cm anterior vaginal wall incision is made at the level of the midurethra. The dissection is then carried out laterally to the level of the inferior pubic rami on either side using blunt and sharp dissection. This surgical preparation provides a pathway for the delivery of the sling arms. The polypropylene mesh tip is placed onto an introducer, which is inserted into the dissected pathway and used to pass the distal arm anchors through the obturator internus muscle behind the pubic ramus. The sling is advanced using the introducer until the midline of the sling reaches the patient's midline under the urethra. This placement of the sling tip is repeated similarly on the opposite side. The polypropylene mesh sling is then brought to rest under the midurethra in a tensionless fashion. The anchors of the sling are resting in the obturator internus muscle. The goal of the surgeon is to visually see the periurethral tissue "pillowing" through the mesh material with a potential space existing between the sling and urethra such that a small instrument could easily be inserted. Cystoscopy is performed to ensure the bladder, urethra, and ureters are not compromised. The vaginal incision is then closed with a running absorbable suture.

## CLINICAL STUDIES

There have been a tremendous number of articles written on the Single Incision technology. The early articles using SIS were mixed, and most early findings pertaining to their efficacy did not show equivalence to the results of the transobturator and retropubic slings<sup>[4]</sup>. Walsh<sup>[5]</sup> showed in 2011 that the use of the TVTsecure sling resulted in cure rates of 76% both subjectively and objectively. He described using both a "U" approach and a hammock approach. He concluded that more studies are needed before TVT secure could be routinely used. There were other slings such as the Ajust sling by C.R. Bard, Inc., New Providence, NJ United States, that conceptually made sense and, if used in the appropriate hands, yielded high success rates. In Jiang *et al*<sup>[6]</sup> paper, he showed that using the AJust sling resulted in subjective and objective cure rates of 82.3% and 91.2% in a 12-mo follow-up respectively. This was a single site study where there were no cases of bladder perforation or major bleeding. There were also no reported cases of groin pain at 6 and 12 mo<sup>[6]</sup>.

This study exemplifies the importance of technique when placing the SISs. Although this group of researchers was able to achieve high success rates with this sling, the sling was not universally deployed successfully, and, as a result, this sling even with its high success rates is no longer being marketed by C.R. Bard Inc.

Initially, the SIS was thought to work differently than other slings and its placement and tensioning were not standardized. Surgeons were using it to go in the



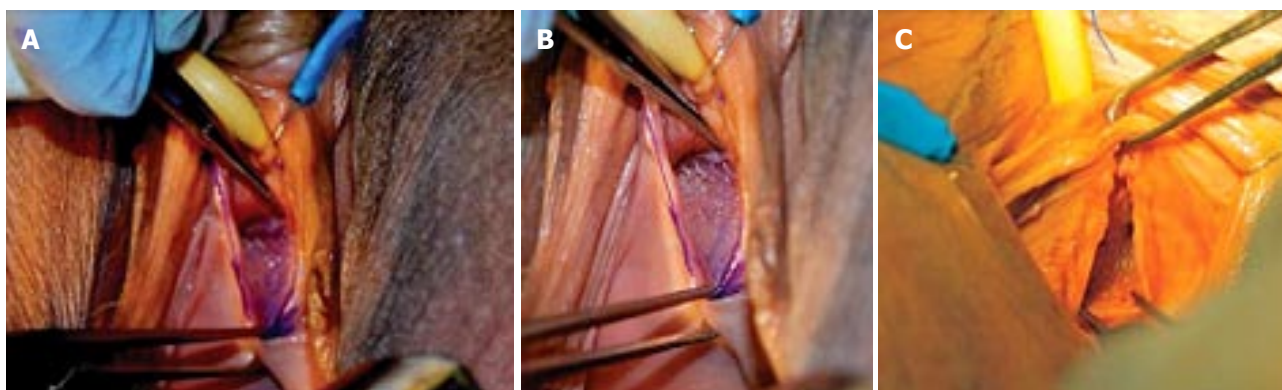


Figure 1 Placement of mid-urethral slings to alleviate stress urinary incontinence using the (A) retropubic; (B) transobturator; (C) single incision techniques.

retropubic direction as well as the obturator location. It then became accepted by most that the placement was to be in the obturator internus muscle. The tension could be set in many different ways, but the end result would be a sling that was up against the urethra with the periurethral tissues “puckering or pillowing” through the mesh openings such that a potential space existed to insinuate a small medical instrument between the urethra and the sling (Figure 1).

In the article entitled “Cadaveric Assessment of Synthetic Mid-Urethral Sling Placement”, the placement of the SIS was compared to the obturator and retropubic sling<sup>[7]</sup>. It was determined that the SIS was similar to the others in appearance and furthermore was most likely at the midurethra and had the most correct tension. It is studies like this that show what is being done by the three sling approaches have different means of achieving the same endpoint.

There are presently around 26 randomized controlled trials, which are using 7 different types of SISs. In these studies approximately 3300 patients were evaluated<sup>[8]</sup>.

Many of the studies have been performed comparing the SIS to the standard mid-urethral slings, which are considered to be either obturator slings or retropubic slings. The majority of these studies support the use of the SIS<sup>[9-25]</sup>. Lee *et al*<sup>[25]</sup> recently published a randomized trial comparing single incision vs outside-in transobturator mid-urethral sling. This paper studied the MiniArc SIS and showed an objective cure rate of 94.4% and a patient reported cure of 92.2% at 12 mo. The Monarc sling was the comparator to the MiniArc and it showed statistically similar results with a 96.7% objective cure and a 94.2% subjective cure. The operative time was reduced by 0.5 min in the SIS group. The Monarc group required more analgesia in the first 24 h and reported more short-term groin pain. The quality of life questionnaires and sexual function questionnaires revealed similar results in both groups. The patients undergoing repeat incontinence surgery were 2.7% in the MiniArc group compared to 1.8% in the Monarc group while 6.2% of the Monarc group had groin pain beyond 6 mo compared to 0% in the MiniArc group. For both patient groups, BMI and age were

associated with higher failure rates<sup>[25]</sup>.

Similar data was shown by Enzelsberger *et al*<sup>[26]</sup> who also looked at the MiniArc SIS and compared it to the Monarc. In this study, there was an objective cure rate of 82%. They also had shorter OR times and less groin pain. In our long-term study using the Solyx SIS, we also saw subjective success rates of 93% over a mean follow up of 43 mo<sup>[27]</sup>. There was, however, one recent article by Basu *et al*<sup>[28]</sup> that showed a lower success rate with the SIS than an obturator sling. This study also had a higher erosion rate with the SIS, which possibly implies a technical issue with using the single incision technology<sup>[28]</sup>.

In the Mostafa *et al*<sup>[8]</sup> metaanalysis, he primarily looked at the MiniArc sling as compared to either retropubic or obturator slings. This study shows an aggregate objective cure rate of 88% with a subjective cure rate of 76% for the SISs. Additionally, the SIS had shorter operative times, lower incidence of groin pain, earlier return to work, and lower pain scores. There were no significant differences in subjective or objective cure rates for the SIS vs the standard mid-urethral slings. Also, the impact on quality of life and sexual function were similar. The TVT secur was not included in this analysis due to its poor early data and that it is now off the market as of 2012.

## CONCLUSION

There are many SISs currently available. Each is different in its design and applicator as well as technique for placement. They all hope to provide the same endpoint, which is a backboard for the urethra to use with increases in abdominal pressure. Current data does suggest that if the SIS is used appropriately there would be an enhanced safety profile with less postoperative discomfort and high success rates. It is the responsibility of the medical community to provide guidelines for the use of these slings and to standardize their placement to assure reproducibility of the success rates. The correct use of SISs will ultimately lead to a treatment, which provides high success rates with low morbidity for our patients who suffer with SUI.

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