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Outcome of Pregnancy in Saudi Women with Sickle Cell Disease Attending the Tertiary Care University Hospital in Eastern Province of Saudi Arabia

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Abstract

Sickle cell disease (SCD) is a chronic genetic hematological disorder with multiorgan involvement and is associated with complications during the pregnancy. This is a well-known disorder in Saudi Arabia, but no study has reported its outcomes in pregnant Saudi females of the Eastern region. This study was carried out to compare the fetomaternal outcome in patients with SCD with those without SCD. This was a retrospective cohort study done in the Eastern Province of Saudi Arabia in a tertiary care, teaching hospital, by retrieving the data through the code ICD-9 for SCD, the control group was also selected with comparable characteristics. A total of 302 SCD pregnant patients were included for comparison with 600 pregnant women without SCD as control, during the period of Jan 1, 2008 to December 31, 2018. After the data retrieval, percentages of complications were calculated between the study and control groups. Fischer's exact test and t-test were used for statistical analysis by using SPSS version 22. The results showed higher complication rates in pregnancies of patients with SCD. Hypertensive disorders (13.3%), abruptio placenta (1.6%), intrauterine growth restriction (19.2%), thromboembolism (6.6%) and stroke (2.6%) were all higher in SCD as compared to the control group .The complications of SCD itself including anemia (89.4%), acute chest syndrome (13.2%) and sickle cell crisis (39.2%) were also increased during the pregnancy. Both still birth (3.3%) and neonatal intensive care unit admission (1.6%) were also higher in SCD. SCD during the pregnancy is a high-risk situation and can lead to many fetomaternal complications; however, preconceptional counselling, early booking, a careful monitoring during pregnancy and multidisciplinary management approach can prevent potential adverse outcome in this regard. *(Afr J Reprod Health 2019; 23[3]: 42-48).*

Keywords: Fetomaternal outcome, Maternal Complications, Vaso-occlusive crisis, Venous thromboembolism

Résumé

La maladie drépanocytaire (MD) est une anomalie hématologique génétique chronique impliquant plusieurs organes et qui est associée à des complications au cours de la grossesse. Il s'agit d'un trouble bien connu en Arabie Saoudite, mais aucune étude n'a rapporté ses résultats chez les femmes saoudiennes enceintes de l'est du pays. Cette étude a été réalisée dans le but de comparer les résultats fœto maternels chez les patientes atteintes de MD avec ceux ne souffrant pas de MD. Il s'agissait d'une étude de cohorte rétrospective réalisée dans un hôpital universitaire de soins tertiaires de la province orientale de l'Arabie saoudite. Les données ont été extraites du code ICD-9 pour MD. Le groupe témoin a également été sélectionné avec des caractéristiques comparables. Au total, 302 patientes atteintes de MD et enceintes ont été incluses pour la comparaison avec 600 femmes enceintes mais non atteintes servant comme témoin, entre le 1er janvier 2008 et le 31 décembre 2018. Après la récupération des données, les pourcentages de complications ont été calculés entre les groupes d'étude et de témoin. Le test exact et le test t de Fischer ont été utilisés pour l'analyse statistique à l'aide de la version 22 de SPSS. Les résultats ont montré des taux de complication plus élevés lors de la grossesse chez les patientes atteintes de MD. Les troubles hypertensifs (13.3%), une rupture du placenta (1.6%), une restriction de croissance intra-utérine (19.2%), une thrombo-embolie (6.6%) et un accident vasculaire cérébral (2.6%) étaient tous plus élevés chez patientes atteintes par rapport au groupe témoin. Les complications de MD elle-même y compris l'anémie (89.4 %), le syndrome thoracique aigu (13.2%) et la crise de drépanocytose (39.2%) ont également augmenté au cours de la grossesse. Les taux d'admission dans une unité de soins intensifs néonatals (1.6%) et de mortinatalité

(3.3%) étaient également plus élevés chez les patients atteints de MD. La MD pendant la grossesse est une situation à haut risque et peut entraîner de nombreuses complications fœto-maternelles; Cependant, les conseils d'avant-conception, les réservations précoces, une surveillance attentive pendant la grossesse et une approche de gestion multidisciplinaire, peuvent empêcher des résultats défavorables potentiels à cet égard. *(Afr J Reprod Health 2019; 23[3]: 42-48).*

Mots-clés: Issue fœto-maternel, complications maternelles, crise vaso-occlusive, Thromboembolie veineuse

Introduction

Sickle cell disease (SCD) is an inherited hemoglobinopathy affecting many people across the globe. It is associated with fetomaternal morbidities and mortalities during the pregnancy. Chronic red blood cell destruction, anemia and hypoxia along with decreased placental circulation seems to be the most plausible explanation for high risk nature of these pregnancies[1]. The origin of SCD is thought to be in sub-Saharan countries[2]. About 300,000 children are born with SCD each year in the world and two third of them are born in Africa[3,4]. It is a lifelong, chronic disorder which can even be life threatening sometimes. However, recent advances in genetic engineering, molecular medicine and pharmacotherapy has generated new medications to treat SCD which has increased the life expectancy of the affected individuals[5].

In obstetrical clinics, a significant number of pregnant patients suffering from SCD are encountered. Although existing guidelines of evidence-based medicine and multidisciplinary team approach has improved the obstetrical outcomes in SCD patients, still their management is a challenging matter due to increased rate of fetomaternal complications. The obstetrical outcome in such pregnancies is affected by chronic anemia, vaso-occlusive crisis, venous thromboembolism, infections, end organ damage and placental insufficiency. All these complications can ultimately lead to decreased fetal growth, preterm deliveries, intrauterine fetal death (IUFD), neonatal morbidities and mortalities[6].

In local context, SCD is one of the highly prevalent medical conditions in pregnant Saudi women. Al Kahtani *et al* reported the prevalence of sickle cell trait to be 25% among the Eastern province[7]. Over the years, it has been observed that many obstetricians consider pregnancy in SCD patients as a high-risk pregnancy. Despite the severity of this condition, the literature shows a paucity of research in this domain. Till date, there are very few studies regarding the obstetrical outcome in SCD, especially in the Eastern region of Saudi Arabia. Realizing the importance, high risk nature, and burden of this disease in pregnancy, this study was conducted to find out the outcomes and impact of this disease in pregnant women at King Fahad Hospital of the University Al-Khobar, a tertiary care centre, Eastern province of Saudi Arabia where many referral cases of SCD are received.

Methods

It was a retrospective cohort study where all pregnant SCD patients with homozygous status (HBSS) who came for antenatal care or delivered at King Fahad Hospital of the University Al-Khobar, were included. Most of the SCD patients were referral cases who presented in their first or second trimester of pregnancy. Almost all of them were already diagnosed with SCD but in few cases hemoglobin electrophoresis was performed to confirm their status. The data was retrieved by using International Classification of Diseases, 9th Revision (ICD-9) from Jan 1, 2008 to Dec 31, 2018. Only Saudi nationals with singleton pregnancies were included. Twins and other multifetal gestations were excluded to avoid confounding errors. 302 Saudi women with homozygous (HBSS) disease were included; and sickle cell traits as well as other hemoglobinopathies were excluded from the study. Epidemiological data including age, parity, education, HBSS status was also recorded in the study.

Six hundred Saudi women with normal hemoglobin phenotype were selected at random matched with same age, parity and singleton

pregnancy who served as control. Antepartum, intrapartum and postpartum follow up was retrieved from the data, antenatal, delivery and discharge registers as well, with special attention to any fetomaternal complications. Data regarding the complications was calculated as percentages. To calculate and compare the difference in complications between the study and the control groups, Fischer exact test and student t-test was applied by using the SPSS version 22. A P-value ≤ 0.05 was considered to be significant.

Results

Demographic features

During the period of study, 25,830 deliveries occurred in the hospital including both vaginal and cesarean sections, out of which, 302 were found to have SCD with incidence of 1.16% (Table 1). Most of the pregnancies were in the age bracket of 21-34 years (79.4%), 7.2% were ≤ 20 years and 13.2% in women ≥ 35 years. Regarding the parity, 52.9% were nulliparous, and 47 % were multiparous. The body mass index (BMI) in SCD, 225(74%) women had normal BMI, 52(17.2%) were overweight, 15(4.9%) were obese and 10(3.3%) were underweight.

Table 1: Demographic features of pregnant women with SCD in the Eastern Province, Saudi Arabia

Maternal age in years	Sickle cell disease (n=302)	Control group (600)
≤20	22(7.2%)	50(8.3%)
21-34	240(79.4%)	420(70%)
≥35	40(13.2%)	130(21%)
Parity		
0	160(52.9%)	160(26.6%)
1	56(39.4%)	250(41.6%)
2	34(23.9%)	90(15%)
3	35(24.9%)	60(10%)
≥4	17(11.9%)	40(6.66%)
Body mass index		
Underweight (≤18.5)	10(3.3%)	40(6.6%)
Normal (18.5-24.9)	225(74.5%)	320(53.3%)
Overweight (25-25.9)	52(17.2%)	130(21.6%)
Obese (≥30)	15(4.9%)	110(18.3%)

Maternal complications due to sickle disease

Table 2 shows that pregnancy complications in SCD are more pronounced as compared to the control group. Anemia was seen in 270 (89%) of SCD while it was 70 (11%) in control group (p=0.03). Blood transfusion was required in 280 (92.5%) in SCD while it was 93 (15.5%) in control group (p=0.001). Sickle cell crisis was seen in 120 (39.2%) of SCD patients and none in the control group (p=0.0001). Acute chest syndrome was seen in 40 (13.2%) of SCD patients while none in the control group (p=0.001). Similarly, urinary tract infection (UTI) was observed in 42(13.9%) of SCD patients and 28 (5.1%) in control group patients (p=0.003). Venous thromboembolism was seen in 20 (6.65%) of SCD and 8(1.3%) of control group patients (p=0.002), while stroke was seen in 8(2.6%) in SCD and none in control group patients (p=0.005). Intensive care unit admission was seen in 35 (11.55%) of SCD and none in control group (p=0.003). No maternal deaths were recorded in either group.

Obstetrical outcome in sickle cell disease versus control group

Table 3 shows the obstetrical complications in SCD and its comparison with the control group. Pregnancy induced hypertension was seen in 40(13.2%) in SCD and 25 (4.1%) in the control group (p=0.002). Both preeclampsia and severe preeclampsia had higher prevalence in the SCD as compared to the control group. (p = 0.004 and 0.001 respectively). Pre-term labour (< 37 weeks) was observed in 60(19.8%) in SCD and 7 (4.6%) in the control group (p=0.002). Placental abruption 5 (1.6%) in SCD while it was 2(0.3%) in the control group (p=0.001). Intrauterine growth restriction (IUGR) was also high in SCD 58(19.2%) and 20(3.3%) in the control group (p=0.0001). Induction of labour was higher in SCD 80 (26.45%) as compared to the control group 71(11.8%) (p=0.02). Most of the cases with SCD underwent induction of labour because of sickling crisis, IUGR and hypertension. During

Table 2: Maternal complications in pregnant women with SCD versus the control group in the Eastern Province, Saudi Arabia

Complications	Sickle cell disease (n=302), %	Control (n=600), %	Odd ratio	95% confidence interval	p- value
Anemia	270(89.4%)	70(11.6%)	2.02	1.2-1.9	0.03
Blood transfusion	280(92.7%)	93(15.5%)	2.21	1.25-2.2	0.001
Sickle cell crisis	120(39.2%)	-	0.9	0.09-1.2	0.0001
Painful crisis	72(60 %%)	-			
Hemolytic crisis	48(40%)	-			
Acute chest syndrome	40(13.2%)	-	2.23	2.1-3.2	0.0001
Urinary tract infection (UTI)	42(13.9%)	28(5.1%)	2.5	2.3-2.9	0.003
Venous thromboembolism (VTE)	20(6.6%)	8(1.3%)	2.6	1.9-2.23	0.002
Stroke	8(2.6%)	-	1.9	2.0-3.2	0.05
Admission to intensive care unit	35(11.5%0	-	1.5	1,8-2,2	0.003

Table 3: Obstetrical complications in pregnant women with SCD in the Eastern province, Saudi Arabia versus control group

Complications	Sickle cell disease (n=302) %	Control (n=600), %	Odd ratio	95% Confidence interval	P value
Pregnancy induced hypertension (PIH)	40(13.2%)	25(4.1%)	2.25	0.92-4.86	0.002
Preeclampsia	30 (9.9%)	14 2.3%)	2.25	1.32-3.1	0.004
Severe preeclampsia	15(4.9%)	7 (1.6%)	2.9	2.1-3.5	0.001
Preterm labour less than 37 weeks of gestation	60 (19.8%)	28 (4.6%)	2.9	2-3.1	0.002
Abruption of placenta	5 (1.6%)	2 (0.3%)	1.81	1.9-2.8	0.001
Intrauterine growth restriction (IUGR)	58 (19.2%)	20 (3.3%)	1.8	1.2-2.9	0.0001
Normal vaginal birth	192 (63.5%)	500 (83.3%)	1.9	2.1-2.4	0.05
Cesarean deliveries	110(36.4%)	100 (16.6%)	2.1	2.5-3.1	0.004
Induction of labour	80 (26.4%)	71 (11.8%)	2.4	2.8-3.5	0.002
Cesarean section wound infection	26 (8.6%)	16(2.6%)	1.99	2.2.9	0.003
Postpartum hemorrhage	30 (9.9%)	31 (5.1%)	2.9	2.2-3.2	0.05

Table 4: Perinatal outcome in pregnant women with sickle cell disease versus the control group in the Eastern province Saudi Arabia

Outcome	Sickle cell disease n=302	Control group n=600	P value
Fetal anomalies	5 (1.6%)	8 (1.4%)	Not significant
Mean gestational age at delivery	34.8±5 days	38.5±4 days	0.01
Still births	10 (3.3%)	2 (0.3%)	0.001
Average birth weight	2.5±450g	3.32kg ±540g	0.002
Apgar score at 5 minutes (A/S)	7	10	0.01
Mean A/S < 7	20 (6.6%)	11 (1.8%)	0.04
Neonatal intensive care unit admission	25 (8.2%)	12 (2%)	0.001
Neonatal deaths	5 (1.6%)	5 (0.833%)	0.003

labour, the patients were hydrated, kept warm and fetuses were monitored continuously with electronic monitoring of fetal heart rate. The cesarean section rate was higher in SCD 110(36.4%) as compared to the control group 100(16.65%) (p= 0.004). The most important

cause of cesarean section in SCD was fetal distress, IUGR, and abruption of placenta. Postpartum hemorrhage was 30(9.9%) in SCD as compared to 31(5.1%) in the control group (p=0.005). Cesarean section wound infection was higher in SCD 26(8.6%) as compared to the control group 16(2.6%) (p=0.003).

Perinatal outcome in sickle cell disease versus the control group

Table 4 shows the different aspects of perinatal outcome in SCD and the control group. Regarding the fetal anomalies, 5 (1.6%) in SCD and 8 in the control group (1.4%), which means that there is no significant difference between the two groups. Mean gestational age was found to be 34.8 weeks±5days in SCD and 38.6±4 in the control group (p= 0.01). Still births were 10 (3.3%) in SCD and 2 (0.3%) in the control group (p= 0.001). The main causes of still birth in SCD patients were prematurity and abruption of placenta, whereas, in the control group, it was abruption of placenta (one case) and pre-term labour due to multiple congenital anomalies. The mean birthweight was 2.5kg±450grams and 3.32kg±540grams in the SCD and the control group, respectively, (p=0.002). Admission to the neonatal intensive care unit was significantly higher 5(1.6%) in SCD deliveries as compared to the control group5 (0.8%) (p=0.03). The main reasons for higher neonatal admissions were prematurity, IUGR, and respiratory distress syndrome.

Discussion

Pregnant patients with SCD are usually at high risk due to pathological changes in the erythrocytes which make the blood more coagulable. This leads to sickling and clogging of blood vessels as well as placental bed. At the same time hemolysis is another challenging issue in this condition which can cause anemia, thus, making the situation even worse. These pathological changes lead to both maternal and fetal complications. In these cases, an earlier recognition of complications, followed by intervention, is the key to successful obstetric care[7].

The complication usually seen in SCD cases are; sickle cell crisis, deep vein thrombosis, acute chest syndrome, cerebral stroke, anemia and urinary tract infection[8]. A meta-analysis by Oteng-Ntim *et al* has also highlighted the adverse maternal and perinatal outcomes due to SCD and the complications reported are consistent with our findings[9]. The obstetrical complications, such as, hypertensive disorders, preeclampsia, abruption of placenta and deep vein thrombosis increase the chances of preterm labour and cesarean sections in SCD patients, leading to early interventions in the interest of fetus or the mother. Moreover, increased IUGR, low birth weight babies and respiratory distress syndrome have usually been seen in fetuses of such pregnancies. These complications have also been reported by other studies[10-13]. Other medical conditions due to damage to end organs have also been reported in SCD patients which include renal damage, stroke, and venous thrombosis[14-17]. Similar findings have been iterated in the United Kingdom Obstetrics Surveillance system (UKOSS) report which documented that the pregnancy in SCD showed an increased risk of sickle cell crisis, acute chest syndrome and urinary tract infection[18]. These findings have also been observed in our study and are consistent with the previous research.

Many studies have been conducted to find the prophylactic measures which can help in controlling complications in SCD patients. One of which is the prophylactic blood transfusion. Only few non-randomized studies have reported decrease rate in IUGR as a result of prophylactic blood transfusion[19].

The study by Asma *et a*l supported the prophylactic red blood cell exchange transfusion during the third trimester to improve the pregnancy outcome[20]. Sharif also reported decrease in painful crisis after prophylactic blood transfusion[21]. In our study all patients were managed in collaboration with hematologists and the blood transfusion was reserved only for severe anemic cases, hemolytic crisis or other systemic indications, as blood transfusion itself has many

short- and long-term complications. Regardless of this, many authors support the prophylactic red blood cell transfusion in selected cases, such as, SCD patients presenting with history of perinatal death, chronic organ dysfunction, recurrent painful crisis and anemia. This transfusion is usually planned at least 3-4 weeks apart with the targeted hemoglobin of 10-11 gm /dl[22,].

The management of SCD in pregnancy starts from the preconceptional care which includes risk assessment, fitness for pregnancy, comprehensive counselling of couple and an effective contraception. Vaccination for hepatitis, meningococcal and pneumococcus is mandatory during this time to avoid any morbidity and mortality during the pregnancy. RCOG guideline in this respect is a very good source to go for evidence-based management[23]. Moreover, the antenatal care must be multidisciplinary in collaboration with hematologist and other health care professionals. Frequent visits, counselling and fetomaternal monitoring is recommended for reducing maternal and fetal complications.

Planned induction of labour has been strongly recommended and the decision should only be made by the consultant obstetrician. Adequate analgesia, rehydration, patient warming, and active management of 3rd stage of labour and continuous electronic fetal heart rate monitoring can help in getting better outcomes in such cases[24]. Postpartum pain management, treatment of anemia and thromboprophylaxis are also very important in SCD patients. In addition to it, sickle cell status of the baby should also be determined immediately after the birth so that the child can be diagnosed at an early stage and neonatal management can be provided at the earliest.

Conclusion

Sickle cell disease is a chronic multisystem disease and it requires special care during the pregnancy. All such patients should be offered periconceptional assessment and counselling. Antenatal, intrapartum, and postpartum care should be provided with multidisciplinary approach to avoid the complications. Anemia correction, thromboprophylaxis and urgent treatment of infections can avoid fetomaternal complications.

Disclosure

Authors declared that they have no conflicts of interest. This work was non-funded.

Contribution of Authors

YH and NQ, conceived and designed the study. YH collected the data, analyzed and prepared the manuscript. NQ provided the review of manuscript. YH and NQ have revised and approved the final version of the manuscript for the publication.

References

1. Al-Farsi SH, Al-Riyami NM, Al-Khabori MK, Al-Hunaini MN. Maternal complications and The Association with Baseline Variables in Pregnant Women with Sickle Cell Disease. Hemoglobin 2013;37(3):219-26
2. Angastiniotis M, Modell B, Englezos P and Boulyjenkov V. Prevention and control of haemoglobinopathies. Bull World Health Organ 1995; 73: 375–86.
3. Diallo D and Tchernia G. Sickle cell disease in Africa. Curr Opin Hematol 2002;9(2): 111-6.
4. Quinn CT, Rogers ZR and Buchanan GR. Survival of children with sickle cell disease. Blood 2004;103(11):4023–8.
5. Wierenga KJJ, Hambleton IR, Lewis NA and Unit SC. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. Lancet 2001; 357(9257):680–3.
6. Serjeant GR, Loy LL, Crowther M, Hambleton IR, Thame M and Paed DM. Outcome of pregnancy in homozygous sickle cell disease. Obstet Gynecol 2004;103(6):1278–85.
7. Al Kahtani MA, Alqahtani M, Alshebaily MM, Abd M, Moawad A and Aljohani N. Morbidity and pregnancy outcomes associated with sickle cell anemia among Saudi women. Int J Gynecol Obstet 2012;119(3):224–6.
8. Villers MS, Jamison MG, De Castro LM and James AH. Morbidity associated with sickle cell disease in pregnancy. Am J Obstet Gynecol 2008;199(2):125-e1.
9. Oteng-ntim E, Meeks D, Seed PT, Webster L, Howard J, Doyle P and Chappell LC . Adverse maternal and perinatal outcomes in pregnant women with sickle cell disease: systematic review and meta-analysis.

Blood 2015; 125(21):3316–26.
10. Barfield WD, Barradas DT, Manning SE, Kotelchuck M and Shapiro-Mendoza CK. Sickle cell disease and pregnancy outcomes: women of African descent. Am J Prev Med 2010; 38(4):S542-9.
11. Howard J and Oteng-Ntim E. The obstetric management of sickle cell disease. Best Practice & Research Clinical Obstetrics & Gynaecology. Best Pract Res Clin Obstet Gynaecol 2012; 26(1):25-36.
12. Rogers K. Sickle cell disease in pregnancy. Obstet Gynaecol Reprod Med 2019;29(3):61–9.
13. Hanley JA, Negassa A and Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol 2003; 157(4):364-75.
14. Thame M, Lewis J, Trotman H, Hambleton I and Serjeant G. The mechanisms of low birth weight in infants of mothers with homozygous sickle cell disease. Pediatrics 2007; 120(3):e686-93.
15. Muganyizi PS and Kidanto H. Sickle cell disease in pregnancy: trend and pregnancy outcomes at a tertiary hospital in Tanzania. PLoS One 2013; 8(2):e56541.
16. Desai G, Anand A, Shah P, Shah S, Dave K, Bhatt H,Desai S and Modi D . Sickle cell disease and pregnancy outcomes: a study of the community-based hospital in a tribal block of Gujarat, India. J Heal Popul Nutr 2017;36(1)1–3.
17. Barfield WD, Barradas DT, Manning SE, Kotelchuck M and Shapiro-mendoza CK. Sickle cell disease and pregnancy outcomes. AMEPRE 2010; 38(4):S542–9.
18. Knight M, McClymont C and Fitzpatrick K. on behalf of UKOSS. United Kingdom Obstetric Surveillance System (UKOSS) Annual Report 2012. National Perinatal Epidemiology Unit. Oxford; 2012.
19. Gilli SC, Paula EV De, Biscaro FP, Marques JF, Costa FF and Saad ST. Third-trimester erythrocytapheresis in pregnant patients with sickle cell disease. Int J Gynaecol Obstet 2007;96(1):8–11.
20. Asma S, Kozanoglu I, Gereklioglu C, Akdeniz A, Kasar M, Turgut NH,Yeral M,Kandemir F,Boga C and Ozdogu H . Prophylactic red blood cell exchange may be beneficial in the management of sickle cell disease in pregnancy. Transfusion 2015; 55(1):36–44.
21. Sharif J, Byrd L, Stevenson K, Raddats J, Morsman E and Ryan K. Transfusion for sickle cell disease in pregnancy: a single-centre survey. Transfusion 2018; 28(3):231-5.
22. Ngo C, Kayem G, Habibi A, Benachi A, Goffinet F, Galacteros F and Haddad B. Pregnancy in sickle cell disease: maternal and fetal outcomes in a population receiving prophylactic partial exchange transfusions. Eur J Obstet Gynecol Reprod Biol 2010; 152(2):138-42.
23. RCOG Green top guideline no 61. Management of Sickle Cell Disease in Pregnancy. July,2011;(61).
24. Hassell Kathryn. Pregnancy and Sickle Cell Disese. Hematology/Oncology Clinics 2005; 19(5):903-16.