Intra-hepatic Cholestasis of Pregnancy (ICP) or obstetric cholestasis is a pregnancy-specific disorder. Maternal symptoms can be severe and incapacitating, however the clinical course is often benign. A high frequency of pre-term labor and delivery and stillbirth of unknown origin has been reported. Recently, ICP has been described as a "puzzling disorder" because of its clinical presentation and epidemiology, the absence of well-known etiological factors and the unexplained fetal compromise.\(^1\)

The objective of IRIS project is to improve knowledge about the factors that compromise fetal well-being. Specifically, it will collect international maternal and fetal clinical data about ICP-related stillbirth. We encourage readers to report their experience and join our effort.

This article summarizes the current knowledge about ICP. We review clinical features of the disease, etiology, maternal and fetal risks, and treatment.

**CLINICAL, PATHOLOGICAL AND EPIDEMIOLOGICAL FEATURES**

Intra-hepatic Cholestasis of Pregnancy is characterized by generalized pruritus (mainly in palms and soles), that is of nocturnal predominance and not associated with skin lesions. Its onset usually begins in the third trimester of pregnancy, remains until the end of the gestation and disappears a few days after delivery. In a subset of patients (in approximately one of six who develop ICP), one observes mild jaundice and
ETIOLOGY

The precise etiology of ICP is still unknown, although a genetic predisposition to the disease has been proposed. In such predisposed women, the increased estrogen levels that occur during pregnancy could cause an intra-hepatic cholestatic disorder.

A. The Role of Estrogen in ICP

While there are significant epidemiological, clinical and basic science data to support an etiological role for estrogens, the molecular mechanism of such an association remains unknown. Some clinical observations that support the role of estrogen include:

(i) the temporal relationship between the onset of the disease and estrogen levels during gestation (onset of ICP is highest in the third trimester when estrogen production is at its maximum),
(ii) the observation that ICP is five times more frequent in twin pregnancies which, by nature, have higher levels of estrogen, and
(iii) the observation that pregnant patients with ICP who, after delivery use oral combined contraception, frequently develop similar clinical symptoms.

In male and female volunteers without ICP, estrogens induce a reversible decrease in the hepatic clearance of sulfobromophthalein. Sulfo-bromophthalein is excreted by the same anion transporters that secrete bile acids. Therefore, the changes evoked by estrogen in the non-pregnant state may provide clues to what occurs during pregnancy when estrogen concentrations are high. The intensity of the estrogen-induced cholestatic change is greater in women with past histories of ICP than in controls. Moreover, women and men whose sisters or mothers had ICP also presented an exaggerated response to the estrogen challenge. These observations support the notion that there is some familial susceptibility to estrogen-induced cholestatic change.

However, the exact nature of this association is presently unknown.

At the molecular level, estrogen may act at the baso-lateral side of the hepatocyte to decrease membrane fluidity, alter protein function or induce a disruption of the structural and functional integrity of the hepatocellular tight junction, thereby...
causing dysfunction in the excretory pathways to the bile duct.\textsuperscript{8, 9}

We have shown that there are no differences in levels of plasma estradiol or progesterone levels between patients with ICP and those with normal pregnancies.\textsuperscript{10} New evidence indicates that the maternal plasma levels of DHA, the estriol precursor of fetal adrenal origin, is decreased in the plasma of patients with ICP which causes decreased placental synthesis of estriol.\textsuperscript{11} The exact nature and the consequence of a decreased fetal adrenal endocrine function, coupled to a decrease in estriol production remain to be determined.

The current appreciation of the role of estrogen is that patients who develop ICP have an abnormal hepatic reactivity to the physiological rise in plasma levels of estrogens during pregnancy.\textsuperscript{1, 5} It has also been suggested that progesterone or an associated metabolite may be causally related to ICP. Although patients with ICP appear to have normal progesterone synthesis, there are reports that their plasma levels of sulfated progesterone metabolites are increased.\textsuperscript{1, 4, 12} Whether the changes in progesterone metabolism cause the hepatic cholestasis or are a consequence of the cholestasis remains unknown.

B. The Role of Genetics in ICP

Observations that support a genetic mechanism for ICP include:

(i) a markedly higher prevalence of ICP in some countries, particularly in a population of Chilean aboriginals,

(ii) the observation of a higher frequency of ICP in women with mother or sisters with a positive history of ICP,

(iii) the observation of cases of ICP presenting within the same family, recorded in family pedigrees.\textsuperscript{13} Studies on HLA haplotype distribution failed to demonstrate a relationship between patients with history of ICP and HLA.\textsuperscript{14} Also a study on Class II HLA alleles found no differences between ICP and controls.\textsuperscript{15}

C. The Role of Environmental Factors in ICP

An as yet, unidentified environmental factor has been suggested as the cause of ICP. This suggestion is based on the observations that:

(i) only 60\% of patients who develop ICP will develop the condition in a subsequent pregnancy,

(ii) the intensity of cholestasis changes during pregnancy, and

(iii) the prevalence of the disease has a geographical and seasonal distribution, with more cases occurring during the spring.\textsuperscript{1, 6}

Several causal environmental factors have been proposed and include pollutants present in pesticides, erucic acid (a long chain monounsaturated fatty acid) that is present in rapeseed oil\textsuperscript{1} and a diet deficient in oligo-elements such as selenium.\textsuperscript{16}

Data regarding the etiology of ICP is diverse and inconclusive. It appears that there may be genetic predispositions to the disease. Genetically predisposed women have an abnormal hepatic reactivity to external factors, including estrogens. The increased levels of estrogen that occur during the third trimester of pregnancy may trigger the disease.

MATERNAL AND FETAL IMPACT OF ICP

Intra-hepatic cholestasis of pregnancy is a liver disease that has systemic consequences. A though of minor consequence to maternal health, ICP creates significant fetal risks.

A. Maternal Consequences of ICP

Elevated plasma prolactin concentration, changes in carbohydrate metabolism and altered renal and intestinal function have been reported in patients with ICP.\textsuperscript{17-19} Steatorrhoea and a decrease in vitamin K-dependent clotting factors have been also reported. These alterations are uncommon, mild and transient. Severe or persistent liver failure has not been reported after an episode of ICP.

Continued on page 4
B. Uterine and Placental Consequences of ICP

A significant increase in uterine contractile activity has been demonstrated during the course of the disease, an event that has been associated with the high incidence of spontaneous pre-term labor.\(^{20}\) Reduced activity of steroid- and xenobiotic-metabolizing enzymes in placentas from patients with ICP has been demonstrated.\(^{21,22}\)

C. Perinatal Consequences of ICP

There is a well-known but poorly understood association between ICP and poor perinatal outcome. A higher incidence of clinical markers of intrauterine asphyxia, such as meconium staining of amniotic fluid (25% to 45%) and fetal distress (12% to 22%) have been reported in pregnancies with ICP.\(^{23,24}\) Since the first case report of ICP in 1851 that described a woman with a history of recurrent ICP and pre-term delivery,\(^{25}\) numerous publications have reported the association between ICP and spontaneous pre-term labor.\(^{4,23,24,26,27}\) The reported risk of pre-term delivery from descriptive and non-controlled studies is as high as 44%. In a large series from our center, we reported that the risk for spontaneous pre-term delivery in patients with ICP was four times greater than for pregnant controls (Odds Ratio [CI95%] 3.98 [1.96 to 8.22, \(p<0.05\)).\(^{23}\)

ICP is a strong risk factor for pre-term delivery. The risk of pre-term delivery is associated with precocity of ICP presentation, duration of disease, degree of hepatic dysfunction and with the presence of maternal jaundice, which suggests that a longer evolution or greater duration of severity of ICP may increase the risk of prematurity.\(^{4}\) The molecular mechanism responsible for ICP associated pre-term delivery is poorly understood, however a role for bile acids has been suggested.\(^{28-30}\)

A high incidence of fetal death has been described in pregnancies with severe ICP. The reported frequency of ICP-related stillbirth may be as high as 35%, which is double that of the general population.\(^{24}\) The authors of most reports about gestational ICP are unable to explain the resulting stillbirth. Typically, the fetuses of ICP pregnancies grow normally and there are often normal surveillance tests in the week prior to the stillbirth.\(^{21}\) Meconium in the amniotic fluid may be the only reportable clinical sign.

In an in vitro model, bile acids, in similar concentrations as reported in patients with ICP, are capable of inducing contractions of the chorionic vessels. This supports, in part, the hypothesis that bile acids (present in elevated concentrations in the meconium) may induce spasms of the chorionic vessels,\(^{32}\) which in turn decrease fetoplacental blood flow thereby causing acute fetal asphyxia. A direct toxic effect of meconium on the umbilical cord vessels has also been reported.\(^{31,34}\) However, several publications have not reported any abnormalities in umbilical artery Doppler studies in patients who present with ICP.\(^{35,36}\) At this time, there appears to be no convincing evidence on which to postulate a role for meconium as the mechanism for the unpredictable fetal deaths.

In order to evaluate the perinatal outcome of ICP, we prepared a meta-analysis of the reported studies published from 1960 until February 2000 (unpublished data). We reviewed all clinical reports of ICP and pregnancy outcome and included only those wherein no pregnancy intervention occurred, those with an identified control group and a methodology that evaluated the rate of prematurity, fetal growth restriction and perinatal outcome. Four well-designed and controlled studies evaluated 541 patients with ICP and 597 controls.\(^{23,24,27,31}\) The data demonstrate that those patients with ICP have a greater frequency of pre-term delivery, stillbirth and perinatal mortality. There were no significant differences in the frequency of neonatal mortality or the frequency of fetal growth restriction (Table 1).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio [95% confidence interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term birth</td>
<td>2.10 [1.47 to 3.0]</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>0.89 [0.62 to 1.27]</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>5.65 [1.58 to 30.6]</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>5.99 [1.93 to 24.1]</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>6.68 [0.8 to 3.07]</td>
</tr>
</tbody>
</table>

Table 1. ICP and Perinatal Outcome.
TREATMENT

Currently there is no known treatment for ICP, with the exception of delivery. Many drugs, such as cholestyramine, phenobarbital, s-adenil methionine and epomediol have been previously tested in clinical studies, however they have produced only slight symptomatic relief, minor improvement in hepatic function and have not improved fetal outcome. Recently, small but encouraging studies suggest that the oral use of ursodeoxycholic acid may prevent the adverse fetal outcome of ICP. However its efficacy requires evaluation in large controlled clinical trials.

The neonatal effect of ICP is purely a function of its effect on the fetus. In current clinical practice, even in the absence of a specific treatment for this condition, careful fetal assessment and appropriate and timely medical intervention have improved perinatal outcome. In our center, we regularly monitor fetal activity, perform weekly non-stress tests starting at the time of diagnosis of ICP, and, in the absence of a contraindication, induce labor at 38 weeks gestation. In those patients with jaundice, the interruption will be planned by 36 weeks after evaluation of lung maturity by amniotic fluid test. The considerations regarding method of delivery or fetal monitoring during labor are no different for this population of patients than they are for the normal population.

IRIS PROJECT

The clinical features of ICP and its perinatal consequences have been thoroughly characterized. However the mechanism of ICP-related perinatal risk has not been elucidated. Regarding the high incidence of pre-term delivery, there is some evidence to support a role for a bile acid-induced increase in uterine contractile activity and resultant pre-term birth. However, we lack such evidence to postulate a role for bile acid in the ICP-related stillbirth. Furthermore, since ICP and ICP-related stillbirth present infrequently in one institution, it will be difficult for any one group to test any hypothesis in their center alone. A collaborative multi-center initiative is necessary.

The objective of IRIS (International Registry of Intra-hepatic Cholestasis of Pregnancy related Stillbirth) is to promote the international collection of data for cases of ICP-related stillbirth. The collected data will allow us to generate and test new hypotheses about the etiology of ICP-related stillbirth, identify a reliably predictive clinical marker for this outcome and eventually plan a strategy for its prevention.

We invite international physicians and patients to join the registry and submit their data of ICP-related stillbirth cases. We maintain a database at <http://escuela.med.puc.cl/iris/welcome.html> that allows easy entry and secure and reliable transmission of the information. We invite you to visit and evaluate the site and contact the study coordinator for more information.

The New Case Report form requires the following data:

- information about the reporter (Physician’s name, telephone and fax numbers, Email address),
- information about the patient (identifying characteristics, year of birth, countries of birth and residence),
- maternal illness independent of pregnancy
- data regarding previous pregnancies (maternal illnesses including itching, premature rupture of membranes, premature onset of labor, pregnancy-induced hypertension)
- data regarding index pregnancy (degree of control, maternal jaundice, gestational age when itching started, laboratory tests [indirect bilirubin, total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, serum amylase], hospitalization for premature uterine contractions, gestational age at delivery, weight of stillbirth, length of stillbirth, malformations, placental abnormalities, additional comments)

Although at the present time, our database only contains data regarding our own cases, we hope to receive 50 international reports per year and will report our observations and conclusions routinely. We expect new hypotheses to arise after our preliminary analysis of the first 200 cases.
REFERENCES


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Understanding the Effect of Domestic Violence on Pregnancy, Labour and Delivery

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Introduction

Because the issue of violence against women is such an important social problem with serious health consequences for abused women and their children, health professionals providing care to pregnant women need to consider how the experience of abuse in current or past intimate relationships could affect their patients during pregnancy, labour, and delivery. This paper reviews current evidence from the medical, nursing, and midwifery literature, with a particular focus on clinical issues, and identifies some important, but as yet unresolved issues. For a more comprehensive analysis of these issues, readers are referred to other materials, some of which are listed in the bibliography.

For the purposes of this paper, we use the terms violence and abuse interchangeably, to mean the use of physical force and verbal threats to intimidate another person with whom one has an intimate or other close family relationship. The abuse can manifest as physical, psychological, or sexual abuse.

Why Violence against Women is an important Health Issue

In a 1993 Statistics Canada survey of 12,300 adult women, 29% of the women who had ever been married or involved in common-law relationships reported that they had been assaulted by their partners and 51% reported at least one incident of physical or sexual violence since the age of 16. Younger women (18 to 24 years), women whose household incomes were less than $15,000, and women whose marriages (or common-law partnerships) had lasted less than 2 years reported higher rates of abuse; neither educational level nor geographic location was associated with variation in the rate of abuse. When asked about the occurrence of violence in association with their pregnancies, 21% of women abused by a partner reported being assaulted during pregnancy.

The incidence of physical abuse in pregnancy has been examined in two Canadian studies. When women receiving prenatal care from family physicians and obstetricians working in either private, community-based, or university teaching clinics in Toronto were asked about their experience of physical abuse in pregnancy, 6.6% reported physical abuse during the current pregnancy and 11% reported being abused prior to the current pregnancy. Similarly, a recent study of pregnant women attending a publicly funded, community-based health program in Saskatoon found that 5.7% reported physical abuse during pregnancy and 8.5% reported experiencing abuse in the year prior to their third-trimester interview. The risk of abuse for this group of women was greater if they were aboriginal, if their partners had a problem with alcohol, and if they had high levels of perceived stress in the preceding year.

Numerous studies have shown that abuse accounts for a substantial proportion of the injuries that bring women to hospital emergency departments. Abused women are more likely to present with physical symptoms, such as headache, irritable bowel syndrome, and chronic pelvic pain, than nonabused women. The prevalence of psychological problems, such as depression, suicidal behaviour, and substance abuse, is higher in abused women as well.

Looking at 1992 Canadian homicide statistics, spousal homicides accounted for 17% of solved murders, with men killing their wives in 84% of these cases and women killing their husbands in 16% of cases; 42% of family-related homicides involved a history of domestic violence reported to police. During the period from 1974 to 1987, 31% of men who killed their wives went on to commit suicide immediately following the incident.

Although a systematic review of the literature found no consistent relationship between violence during pregnancy and adverse pregnancy outcomes, some of the studies reviewed did find a difference between abused and nonabused women's outcomes of pregnancy in mean birth weight and incidence of low birth weight. Both direct and indirect causal pathways have been postulated to explain such adverse outcomes.

Blunt trauma to a maternal abdomen has been shown to lead to placental abruption, preterm labour and delivery, fetomaternal hemorrhage, and fetal death. Assaults resulted in more pregnancy complications than motor vehicle accidents or falls, the two other major causes of trauma during pregnancy.

Physical, sexual, or emotional abuse during pregnancy can lead indirectly to adverse pregnancy outcomes by affecting pregnant women's health behaviours. For example, abuse during pregnancy has been associated with delayed entry into prenatal care, increased behavioural risks such as the use of tobacco, alcohol, and illicit drugs, and poor maternal nutrition, all of which have been associated with...
increased risk of low birth weight and preterm delivery.10,18,19

Labour and delivery can be particularly difficult for women with a history of sexual abuse, and physicians and other birth attendants unaware of the abuse could have difficulty understanding their seemingly unusual behaviour. As labour progresses, the increasing pain, the subsequent sense of loss of control, and the repeated pelvic and genital examinations by multiple caregivers can result in unexpectedly extreme responses from labouring women* from too quiet and passive to screaming, crying, or uncontrollable terror. Other women respond by becoming overly controlling or demanding. Still others dissociate during labour or delivery. Some accoucheurs have even speculated that a history of abuse plays a role in inadequate fetal descent and prolonged second stage, based on their interactions with abused women during labour.20

Role of the Caregiver

How to identify women with a history of abuse

Screening. Because of the high prevalence of abuse in the general population, all pregnant women should be screened for past or current history of abuse. Rates of disclosure might be improved if women are asked about abuse at the same time that they are asked about other social risk factors. Some clinicians prefer to ask about abuse during history-taking, while others prefer to use standardized tools. The Woman Abuse Screening Tool is reliable and valid and has been shown to be effective in identifying abuse in adult women patients attending their regular family physicians for prenatal care or periodic health examinations or for assessment of particular health problems.21 It has been included in the Antenatal Psychosocial Health Assessment (ALPH A) form,22 an evidence-based screening tool that can be used as a checklist for psychosocial enquiry and will soon be incorporated into the Ontario Antenatal Record. Women should never be asked questions about abuse in the presence of their partners.

Red flags. Caregivers might be particularly alerted to the possibility of abuse in the following clinical situations.

- Unwanted pregnancy
- Teenage pregnancy
- Delay in seeking prenatal care
- Inadequate attendance at prenatal education
- Recurring or unexplained psychosomatic illness
- Addiction to alcohol, tobacco, or psychotropic drugs, or use of illicit drugs
- Unexpected injuries, particularly to the breasts and abdomen
- History of psychiatric illness

Barriers to identification and disclosure. Women might be reluctant to disclose a history of abuse for a variety of personal and social reasons (eg, shame, embarrassment, uncertainty about housing or financial options, etc) or because previous attempts at disclosure were met with disbelief or denial by other professionals or by family members or friends. Health care providers might be reluctant to ask about abuse because of a lack of understanding of the importance of abuse as a health issue or a lack of information about community resources. Caregivers’ own experiences as victims, perpetrators, or child witnesses to abuse could also affect their readiness to ask about abuse.

What to do on disclosure

When patients disclose a history of abuse, it is crucial that health care providers respond in a way that makes these patients feel believed and supported. It is not appropriate to question behaviour during the abusive episodes or to minimize the seriousness of the abuse. Patients should be provided with information about how to get help in dealing with their experiences.

Trauma management

In situations where pregnant women have sustained direct trauma to the abdomen, continuous fetal heart rate monitoring and external tocodynamometry are recommended. Controversy exists over the duration of monitoring; recommended times range, from 30 minutes23 to 48 hours.26 Women who are Rh negative require Rh globulin.26,27

Referral and collaboration with other physicians, allied health professionals, and community agencies

Some abused women will need help in making changes in their lives as they sort out their experiences of abuse. In addition to providing clinical care, which might include helping them with their physical and psychological symptoms and providing support, health care providers might decide to refer such patients to other health care professionals or to community agencies for assistance in obtaining shelter, sorting out financial options, exploring legal options, and arranging further psychological counseling for themselves and their children.

Safety issues

When abuse is disclosed, the importance of having a safety plan should be stressed by health care providers or other helpers from the community. Many community agencies can provide written materials to help women develop safety plans. If there are children in the family, health care providers should enquire about whether they have ever been abused or if there is risk of abuse and determine whether the physical and emotional environment is safe for the children. Any concerns about the safety of the children must be reported to the appropriate child protection agencies.

Caring for other family members

Family physicians typically provide medical care to members of pregnant women’s families as well and might find themselves caring for partners or other family members who perpetrated the violence. In such situations, physicians
must ensure that the needs of the abused women and the perpetrators are addressed independently, such that their rights to autonomy, confidentiality, honesty, and quality of care are maintained.\textsuperscript{26} Couple or marital therapy is contraindicated unless the woman’s safety can be ensured and the man has taken responsibility for his abusive behaviour.

If current abuse is disclosed, accoucheurs will need to determine whether the home environment is safe for a newborn (and for other children) and whether the woman and her partner are physically and emotionally able to care for a newborn appropriately.

**Confidentiality and Reporting Issues**

Women will feel more comfortable disclosing if they know that the details of their disclosure will be kept confidential by caregivers. This is particularly important for family physicians who also provide care to other family members. Practitioners who are concerned that a history of abuse might affect their patients’ tolerance of certain procedures (eg, transvaginal ultrasound) should check with their patients about what information can be disclosed to these other caregivers (eg, obstetrical consultants, delivery room nurses).

Practitioners are not obliged to report past or current episodes of abuse, no matter how violent. Practitioners should, however, be aware of the recommendations of their provincial colleges with respect to the duty to warn in situations where they become aware of a serious risk of violence to a third person.\textsuperscript{29} If the possibility of child abuse arises, practitioners must inform local child protection agencies of their suspicions.

**Documentation**

As in any clinical situation, disclosures of abuse and relevant positive and negative findings on physical examination should be well documented.\textsuperscript{30} Good records of repeated injuries or recurrent vague complaints might help physicians consider the possibility of abuse, even when women are reluctant to disclose. Moreover, thorough documentation might obviate the need for a court appearance should the case come to trial.

Exactly what information should be recorded on the standardized antenatal record forms that are sent to the delivery room remains unclear. A history of violence before or during pregnancy can affect labour and delivery, but women might not want staff in the delivery room to know about their experience because they do not have long-term, trusting relationships with those caregivers. It is important that caregivers check with their patients about what information to share with other caregivers.

**Future Directions**

**Clinical research**

**Prevalence.** Because the frequency of an event is an important consideration in deciding whether to screen, it would be helpful for practitioners to have accurate, current estimates of the prevalence of violence in Canada, with attention to specific populations. We need to determine regional, social, and cultural differences that would assist policy planners and clinicians to provide better service to abused women and their families.

**Clinical clues and risk factors for violence.** Practitioners would be helped by more research into the clinical clues that suggest violence is an issue in their patients’ lives, including important risk factors.

Given the increasing numbers of refugee and immigrant women coming to Canada, practitioners require more information about their needs. We need to know how to ask about abuse in a culturally sensitive fashion and how best to serve women with violence issues complicated by language barriers, immigration status problems, poverty, and isolation. Little attention has yet been addressed to meeting the needs of these particular women.

**Clinical outcomes.** More research is needed on the effect of violence on pregnancy outcomes. Attention is required to the particular physiologic mechanisms through which violence could affect pregnancy outcomes. In addition, little is known about the effect of aspects of our clinical care; for example, do violence-screening strategies help or hinder our patients? In a recent editorial, MacMillan emphasized the need to expand the extensive work on low birth weight to include an examination of its association with abuse during pregnancy.\textsuperscript{31} In addition, she stresses the need for a population-based study to determine the long-term clinical outcomes for women and their children.

**Roles of caregivers.** Research needs to be done on the roles of various caregivers in identifying and managing domestic violence. Health care is changing rapidly: we are experiencing new kinds of caregivers (nurse-practitioners, midwives), changing types of practice, and increasing mobility of health care providers. With these changes come the challenges of communicating sensitive patient information, such as a history of violence and abuse, to colleagues and sharing care of patients in collaborative ways that best help women and their families.

**Quality of care.** Now that practitioners are becoming more aware of the importance and frequency of violence issues in the lives of pregnant patients, we need to examine how well we are helping these patients. We need to look at how extensively and how sensitively we screen. Are non-abused women intimidated or put off by our style of questioning? Do some screening efforts harm abused women, and if so, which ones?

Questions have been raised about the role of a practitioner’s own gender in his or her ability to help abused women. If there are differences related to a physician’s sex, what can practitioners do to minimize barriers to disclosure or assistance? A nother strongly held belief is that the duration of the doctor-patient

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Domestic continued from page 9

relationship substantially affects disclosure or subsequent management of the problem. If a long-term relationship facilitates disclosure or helps the patient in any way, how can new caregivers short cut the development of a trusting or helpful relationship? Can other professionals or agencies use a family physician’s previously established relationship to enhance their work with that family physician’s patients? On the other hand, does a long-term relationship actually hinder screening, identification, and disclosure? Are practitioners and agencies new to patients better able to help with violence issues?

Further investigation is also needed into patients with multiple problems, eg, patients with a history of abuse who abuse substances. Are we giving these women the comprehensive care they need? Can one practitioner respond to all their needs, and how do we share this type of care with colleagues whose expertise complements our own?

More work needs to be done to determine whether certain interventions are better suited to specific patient populations (adolescents, new Canadians), and whether certain practitioners are better suited to specific roles (family physicians, delivery room nurses, community workers).

Health services research

Financing health care in Canada is undergoing great change. It is unclear how the current fiscal crisis affects practitioners’ abilities and willingness to help abused women. Do time or funding constraints affect our identification, management, and referral of these women, and if so, how? If we take time to screen our pregnant patients for a history of violence, we need to be sure that referring agencies have the capacity to respond to the increased numbers of women seeking their help.

Research is needed into access to health care for women affected by violence. For example, do pregnant or postpartum women recently arrived in shelters have adequate access to medical, nursing, midwifery, or lactation consultant care? We need to know whether practitioners are defining their communities to the best advantage of women affected by violence? Which patients experience access problems due to geographical location, socioeconomic status, ethnicity, or other factors?

A great deal of community service and advocacy work is done after hours by health care practitioners, but this work is often poorly rewarded in any official way. Research into roles and service would enhance this recognition process. It could also invite new members and create new partnerships between community agencies and professionals or among different groups of professionals. Such research would promote public awareness of the extent of violence in our society and the roles and involvement of health care professionals in dealing with this issue.

Finally, although we recognize that health care practitioners are exposed to violence in both their personal and professional lives, little work has been done to explore the extent to which they are affected by these experiences. We need to learn more about self care, coping strategies, peer support, and supervision of patients with difficult problems.

Education

Professional education. Learners need to become familiar with the manifold presentations of violence and to become comfortable talking with patients about abuse. They need to be ready to refer to appropriate helping agencies. They need to see their preceptors and senior clinicians role model these clinical skills.

Education on violence for health care practitioners needs to be evidence based and properly evaluated. Effective methods for disseminating new findings to clinicians need to be implemented. We need to consider whether this education should be multidisciplinary or with groups of peers, and whether survivors of violence have a role in the education of professionals.

Special obstetrical education programs, such as the Advanced Life Support in Obstetrics (ALSO) and Advances in Labour and Risk Management (ALARM) courses, need to incorporate violence issues directly into the curriculum. Domestic violence should not be marginalized by including it as a subsection of abdominal trauma.

Although all practitioners should be aware of violence issues and be able to assist patients appropriately, some caregivers might be interested in developing advanced skills in this area. Consideration should be given to creating educational opportunities for providing advanced training in psychosocial care of obstetrical patients.

Public education. Strategies need to be developed, in conjunction with community agencies, to assist people affected by abuse and violence to use available community resources. Educational efforts must inform patients that violence in pregnancy is an important health issue and worthy of our attention. A variety of media, including pamphlets and posters in medical offices and hospital delivery rooms, should be used to inform the public of health care practitioners’ awareness of violence as a health care issue and to encourage the public to discuss these issues with their family physicians and other health care professionals.

Evaluation of educational endeavours. Public and professional educational endeavours need to be evaluated. We need to know which strategies have helped women and which have been ineffective or harmful. Involvement of survivors of violence, shelter workers, and other allied health professionals would greatly enhance such research.

Conclusion

Not only can the experience of violence and abuse in past or current intimate relationships affect the physical health and psychological well-being of women and their children, these negative experiences can also play a role in pregnancy outcomes and in labour and delivery. As health care professionals, we need to be aware of these issues and
maintain a high index of suspicion for the possibility of abuse in our clinical work. Because of their long-term relationships with patients and because they focus on both physical and mental health issues with their patients, family physicians are in a unique position to identify patients with a history of abuse. 

As attention to these issues is relatively new, many questions remain unresolved. Collaborative projects with family physicians, obstetricians, midwives, patients, and others who work with abused women will help us all to better understand these women’s experiences and to provide exemplary care.

REFERENCES

Twin-to-Twin Transfusion Syndrome: Do We Really Understand It?

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Twin-to-twin transfusion syndrome (TTTS) occurs in multiple gestations, usually in twin pregnancies, and involves the flow of blood from one twin to the other. It occurs in mono-chorionic twins, who themselves have a very high rate of complications, such as severely pre-term delivery, fetal growth restriction and fetal death. Without treatment, the end-result of TTTS is almost always extreme premature delivery. Even with treatment, the fetal/neonatal death rate ranges between 40% to 60%. Despite much enthusiasm for the available treatments for TTTS, fetal survival rates is far less than optimal. This article will review the latest advances in our understanding of TTTS and will focus on the limitations of our knowledge and the disappointing results of treatment trials.

PATHOPHYSIOLOGY

Until a few years ago, our knowledge of the pathophysiology of TTTS was limited. Recently, ultrasound and Doppler studies of the placenta have contributed new information with which to better understand the complex mechanisms involved. It now appears that vascular connections in the placenta between twins must be present before TTTS develops. Vascular anastomoses are rare in di-chorionic twins, but are present in nearly 100% of pregnancies with mono-chorionic twins. With rare exception, TTTS is present only in mono-chorionic twins and will occur in 5% to 10% of mono-chorionic pregnancies. The progressive nature of TTTS in utero is thought to be due to one twin (the donor) slowly pumping blood to the other (the recipient) through the placental vascular anastomoses. Why TTTS occurs in only a small proportion of mono-chorionic twin pregnancies remains unknown.

Recent studies have improved our knowledge of the pathophysiology of TTTS. In a study of 10 mono-chorionic pregnancies diagnosed with TTTS and 10 mono-chorionic pregnancies without TTTS, Bajoria et al performed immediate post-delivery placental injection studies to characterize placental vascular anastomoses and reported arterioarterial, venovenous and arteriovenous (A-V) anastomoses. The data suggest that vascular anastomoses of the A-V type, which run from the donor to the recipient deep within the placenta and are uncompensated by A-V anastomoses running in the reverse direction, may be one etiological factor for TTTS. Although the findings are a promising new development, the sample size of this study was small. What causes the development of these uncompensated anastomoses is unknown. There is a difference of opinion as to whether TTTS can occur in mono-amniotic twins; if it does it is extremely rare. Bajoria compared these anastomoses between mono-amniotic and mono-chorionic pregnancies and observed a greater number of anastomoses of all types in mono-amniotic pregnancies, which suggests that the syndrome may develop when there is a relative lack, rather than an absolute presence, of these vascular connections.

Recent ultrasound studies have demonstrated that TTTS is a slowly progressive disease. It may initially present as early as 13 gestational weeks, but obstetrical ultrasound will usually detect the syndrome between 17 to 26 weeks. The rule is that progressive oligohydramnios develops in one sac and polyhydramnios develops in the other. Subsequent perinatal complications vary; pre-term delivery may occur very soon after the diagnosis or not until several months later. Death of the fetuses or neonates may be due to pre-viable delivery, severe growth restriction of the donor, hypoplastic lungs in the donor, or high output cardiac failure in the recipient. These confounding factors complicate the analysis of studies designed to evaluate the efficacy of interventions.
ULTRASOUND DIAGNOSIS

The classic findings of discrepancies in birth weight, hematocrit values, and neonatal plethora in the recipient and pallor in the donor do not apply to the prenatal diagnosis of TTTS. TTTS is an ultrasound diagnosis made during pregnancy and recent advances have improved its identification. The hallmarks of its ultrasound diagnosis are (i) mono-chorionic gestation, (ii) same-sex twins identified by ultrasound, (iii) the combination of polyhydramnios in one sac and oligohydramnios in the other sac, and (iv) the persistent finding of a small or non-visualized bladder in the donor and a large bladder in the recipient (Table 1).

First trimester ultrasound should be performed on all patients considered at risk for multiple gestation; those with uterine size greater than dates in the first trimester, those with a family history of multiple pregnancies, those of Nigerian descent (Yoruba tribe), and those who conceived after any form of assisted reproductive technology (including ovulation inducing agents, intrauterine insemination, and in vitro fertilization with embryo transfer). Chorionicity is almost always easily determined in the first trimester by ultrasound by noting the distance between fetuses within the uterus and the thickness of the intervening membrane.

A mono-chorionic gestation can also be identified in the second trimester by the presence of the following signs: a combination of a single placental mass, same-sex fetuses and the lack of the twin peak or lambda sign at the point where the inter-twin membrane meets the placental chorionic plate (Figure 1). Although part of the classic presentation, growth discrepancy is not universally present in TTTS. Normal values for the measurement of amniotic fluid in twin gestations are presented in Table 1. One should also carefully search for fetal anomalies. Serial ultrasound should be performed for any case in which one contemplates a diagnosis of TTTS, but where its criteria are not specifically met, because TTTS may subsequently appear and the distinction between mono-amniotic and mono-chorionic pregnancy needs to be made.

The description, stuck-twin syndrome, is given when one is unable to visualize, on ultrasound, amniotic fluid in the donor’s sac. It may be confused with a mono-amniotic twin gestation, because the inter-twin membrane is closely wrapped against the donor twin and cannot be visualized by ultrasound. If one fetus remains pressed in one place against the uterine wall over the course of one or more examinations, and the character of the movements is constricted, this is likely a stuck twin. One should pay careful attention to the relative placements of the placental cord insertions and the course of the umbilical cords, as these observations may also be helpful in the diagnosis. Unusual presentations can occur and require expertise to diagnose.

<table>
<thead>
<tr>
<th>Table 1. Twin-to-Twin Transfusion Syndrome (TTTS) Diagnostic Criteria Using Obstetric Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Second trimester diagnostic criteria for TTTS</strong></td>
</tr>
<tr>
<td>1. Mono-chorionic gestation</td>
</tr>
<tr>
<td>a. Same gender</td>
</tr>
<tr>
<td>b. Single placental mass</td>
</tr>
<tr>
<td>c. Thin dividing membrane</td>
</tr>
<tr>
<td>d. Lack of twin peak or lambda sign</td>
</tr>
<tr>
<td>2. Abnormal amniotic fluid volume*</td>
</tr>
<tr>
<td>a. One sac with oligohydramnios, deepest vertical pocket &lt; 2.0 cm</td>
</tr>
<tr>
<td>b. One sac with polyhydramnios, deepest vertical pocket &gt; 8.0 cm</td>
</tr>
<tr>
<td>3. Persistent urinary bladder findings*</td>
</tr>
<tr>
<td>a. Small or no bladder visualized in twin with oligohydramnios</td>
</tr>
<tr>
<td>b. Large bladder visualized in twin with polyhydramnios</td>
</tr>
<tr>
<td><strong>B. Ultrasound findings that may be helpful</strong></td>
</tr>
<tr>
<td>1. Estimated fetal weight discordance (&gt; 20% of larger twin’s estimated weight)</td>
</tr>
<tr>
<td>2. Appearance of a &quot;stuck twin&quot;*</td>
</tr>
<tr>
<td>3. Hydrops fetalis (presence of one or more of the following in either twin)</td>
</tr>
<tr>
<td>a. Skin edema (&gt; 5 mm thickness of scalp skin)</td>
</tr>
<tr>
<td>b. Pericardial effusion</td>
</tr>
<tr>
<td>c. Pleural effusion</td>
</tr>
<tr>
<td>d. Ascites</td>
</tr>
</tbody>
</table>

* Serial scanning may be necessary

TREATMENT

Careful antenatal assessment by ultrasound and tocolysis for pre-term labor are considered conservative managements and are generally used as adjuncts to other invasive treatments. Frequent antenatal assessment may provide an iatrogenic decision for delivery, and may prevent death in utero.

A mnio-reduction (serial amniotic fluid volume reduction) is currently the most frequently used treatment and was the earliest therapy available. During an
TTTS continued from page 13

amnio-reduction, one drains amniotic fluid from the hydramniotic sac, generally with an 18- or 20-gauge needle, in order to restore fluid volume to normal. The amount of fluid drained during a single procedure ranges from 1 to 7 liters\(^2\) and multiple procedures may be necessary if the polyhydramnios recurs. Procedure-related complications occur in about 8% of cases and may include chorioamnionitis, pre-term labor and delivery, pre-term premature rupture of the amniotic membranes, and abruptio placentae.\(^2\)

Poorer outcome is associated with early onset of disease and the use of a greater number of procedures.\(^2\)

Septostomy, the most recently developed therapy, is a process during which one intentionally punctures the inter-twin membrane or septum, thereby allowing amniotic fluid to circulate between the two amniotic cavities.\(^2\) An explanation for the efficacy of this procedure is based on the observation that the inter-twin membrane, or septum, which, in some cases, is compressed against the uterine wall by the polyhydramnios in the recipient’s sac and is therefore not easily visualized on ultrasound, was inadvertently punctured during amnio-reduction therapy.\(^2\) This puncture caused the volume of amniotic fluid between the two sacs to normalize, and sometimes lasted for several weeks.

Septostomy is associated with a risk of umbilical cord entanglement (pseudo-monoamniotic twins).\(^3\) Through use of a 22-gauge needle, the complication of a pseudo-monoamniotic gestation has been eliminated.\(^3\) A 1998 publication reported a fetal/neonatal survival rate of 83% from 12 pregnancies that underwent septostomy.\(^3\) A report of 3 failures is a biased comment on the success of septostomy, because each of the three cases presented with pre-term labor;\(^2\) it is well-known that the prognosis for prolongation of gestation is dismal when pre-term labor has begun.\(^2\)

Because of the high mortality rate in TTTS, sacrifice of one twin by removal at hysterotomy (selective termination) has been performed with the hope of eliminating the hemodynamic derangements.\(^3\) Complications of hysterotomy, including pre-term rupture of the membranes, chorioamnionitis, pre-term labor and pre-term delivery, outweigh the possible benefit of this therapy. Percutaneous ultrasound-guided umbilical cord ligation is now an available option and appears to decrease the rate of these complications. The current survival rate for at least one twin in each pregnancy is about 75% to 80% with any therapy.\(^2\) It is too early in the experience of the percutaneous ultrasound-guided cord ligation technique of selective termination to make meaningful comparisons.

**SURVIVAL**

Pregnancies with TTTS vary in severity and in their outcomes; reported survival rates from published studies in the past decade range from 21% to 83%.\(^2\) \(^3\) \(^3\) \(^3\) \(^3\) Even though the claims of the proponents for each type of therapy, survival rates for fetuses in large series of TTTS pregnancies undergoing several therapies do not appear to show any overall difference (Table 2).\(^2\) \(^3\) \(^3\) \(^3\) \(^3\) \(^3\)

The efficacy of different treatments for TTTS has not been systematically determined by randomized controlled trials (RCT). There have been only 3 observational, controlled assessments of any treatment for TTTS; all have compared patients undergoing amnio-reduction to untreated, historical controls.\(^2\) \(^3\) \(^3\) Selection bias favours the outcome of patients treated later in calendar time,\(^3\) \(^3\) \(^3\) and although the p-values ranged from 0.04 to 0.0000001, the risk ratio for fetal or neonatal death is 0.06 to 0.66.\(^3\) Thus, serial amnio-reduction has not been demonstrated to be effective and the efficacy of other therapies for TTTS has not been assessed in a controlled manner.

In the past 2 decades, there have been significant advances in the care of severely pre-term neonates. With each successive publication for each therapy, there appears to be a better survival rate (Table 2), which may suggest that advances in neonatal care contribute to...
the improved survival figures. This is supported by an analysis of the deaths in the 3 controlled studies mentioned above, which reveals that two-thirds were neonatal deaths and only one-third were fetal (Table 3). However, it has been difficult to document any definitive benefit from amnio-reduction. A recent study suggested a possible benefit of amnio-reduction, over and above the increased survival due to advances in neonatal care, but only for those TTTS twins delivered < 27 weeks of gestation. In addition, two observations may suggest that FLOC is beneficial: the first being an improvement in the technical expertise of the operators in more recent series, and the second being an increase in the diagnosis-to-delivery interval.41

Despite these advances in therapeutic technique and promising results so far in the largest and most recent series, overall mortality from TTTS remains near 40%.

**SPECTRUM OF SEVERITY OF TTTS**

Since there is a spectrum of severity associated with TTTS, including patients with “mild” or “pseudo” TTTS in study trials will complicate the evaluation of therapeutic efficacy. Some investigators have suggested that early diagnosis and treatment may improve the outcome of pregnancies with TTTS. This may not necessarily be the case, because cases of pseudo-TTTS (low normal amniotic fluid volume in one sac with high normal amniotic fluid in the other), or cases where only one twin is growth restricted, may have been subjectively diagnosed as early cases of TTTS and included in these treatment trials. Including such cases would skew the interpretation of efficacy since outcomes for pregnancies with pseudo-TTTS appear to be better than for TTTS.42

On ultrasound, there may be differences in amniotic fluid volume between the sacs, differences in estimated fetal weights and differences in thickness of the umbilical cords in cases of pseudo-TTTS, but these subjective findings fall short of the acceptable objective diagnostic criteria listed in Table 1. It is difficult to distinguish pseudo-TTTS from other non-TTTS fetal problems that have similar ultrasound findings, such as growth restriction of one twin with a normal co-twin, or two normal twins with low normal amniotic fluid volume in one sac and high normal amniotic fluid volume in the other. Based on this, the fact that the natural history of pseudo-TTTS is unknown and that invasive treatment may not be necessary, cases of pseudo-TTTS should not be included in the treatment arm of future trials.42 Such trials should adhere to more strict inclusion criteria that are objective and diagnostic.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bebbington10</td>
<td>1989</td>
<td>None</td>
<td>47%</td>
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<tr>
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<td>Amnio-reduction*</td>
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<td>Mahoney34</td>
<td>1990</td>
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<td>20%</td>
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<tr>
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<tr>
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<tr>
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<td>Amnio-reduction</td>
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<tr>
<td>Gonsoulin15</td>
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<tr>
<td>Elliott36</td>
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<td>79%</td>
</tr>
<tr>
<td>Saunders1</td>
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<td>Pinette45</td>
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</tr>
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<td>Fries56</td>
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<td>Reisner56</td>
<td>1993</td>
<td>None</td>
<td>40%</td>
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<td>Ville²</td>
<td>1995</td>
<td>FLOC</td>
<td>52%</td>
</tr>
<tr>
<td>De Lia4</td>
<td>1995</td>
<td>FLOC</td>
<td>53%</td>
</tr>
<tr>
<td>Ville³</td>
<td>1996</td>
<td>Amnio-reduction</td>
<td>50%</td>
</tr>
<tr>
<td>Dennis³</td>
<td>1997</td>
<td>None</td>
<td>50%</td>
</tr>
<tr>
<td>Dennis³</td>
<td>1997</td>
<td>Amnio-reduction</td>
<td>82%</td>
</tr>
<tr>
<td>Mari³</td>
<td>1998</td>
<td>Amnio-reduction</td>
<td>66%</td>
</tr>
<tr>
<td>Saade24</td>
<td>1998</td>
<td>Septostomy</td>
<td>83%</td>
</tr>
<tr>
<td>Zikulnig31</td>
<td>1999</td>
<td>FLOC</td>
<td>64%</td>
</tr>
<tr>
<td>Hecher41</td>
<td>1999</td>
<td>FLOC</td>
<td>61%</td>
</tr>
</tbody>
</table>

* Amnio-reduction used only for maternal respiratory compromise

Continued on page 16
Despite recent knowledge, the cause(s) of TTTS remains uncertain. It remains unexplained why uncompensated A-V anastomoses develop in only a small proportion of mono-chorionic twins, although it is likely that this happens during placental angiogenesis during the first trimester. Determining a specific cause, rather than suggesting that this is a random event, will require intensive study of the first trimester placental microenvironment. Currently this may be possible through clinical use of color and power Doppler ultrasound, although this technology has its limitations.

**ETIOLOGY**

Despite recent knowledge, the cause(s) of TTTS remains uncertain. It remains unexplained why uncompensated A-V anastomoses develop in only a small proportion of mono-chorionic twins, although it is likely that this happens during placental angiogenesis during the first trimester. Determining a specific cause, rather than suggesting that this is a random event, will require intensive study of the first trimester placental microenvironment. Currently this may be possible through clinical use of color and power Doppler ultrasound, although this technology has its limitations.

**RANDOMIZED CONTROLLED TRIALS**

Most lacking are data from randomized controlled trials designed to compare the efficacy of different protocols for treating TTTS. Four have been initiated, and three are still underway, hampered by low rates of subject recruitment.

**SUMMARY**

Although much work remains to be done, fetal outcome continues to improve. The international community needs data from comparative clinical trials and from the in-depth pathological and histological study of mono-chorionic placentas, a presently somewhat neglected area of research.

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**NEUROLOGICAL OUTCOME**

In addition to the mortality associated with TTTS, one must also be cognizant of the fact that neurological injury may occur in survivors of TTTS, often at a rate greater than that associated with other mono-chorionic pregnancies.

Why is this? One possible mechanism is that following one fetal death, an acute cerebral ischemia may cause hypotension and hemorrhage of the surviving fetus into the dilated vascular system of the dead fetus may cause hypotension and cerebral ischemia. However, antenatally-acquired neurological injury has occurred in cases where both twins have survived. A second possible mechanism of neurological injury is vascular sludging in the recipient that results from an extremely high hemoglobin concentration. Thirdly, it is also possible that anemia and hypoxemia, common findings in the donor fetus, may be etiologic factors.

The incidence of antenatally-acquired central nervous system injury in survivors of TTTS may be as high as 18%, which may be a compelling reason to perform cranial imaging studies in the 48 hours after birth and carefully follow the neurodevelopmental outcomes of such infants. When the initial diagnosis of TTTS is made, this high incidence of neurologic injury needs to be communicated to patients during counseling.

**REFERENCES**

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Case Report. A 33 year old G2P1 had a previous child with Meckel Syndrome (MKS). During her first pregnancy, the fetus was found to have an occipital encephalocele and enlarged multicystic kidneys at 19 weeks of gestation. He was born at term and on examination was also noted to have external genital anomalies (hypospadias, bifid scrotum) and a backsloping forehead. The couple was counselled about the autosomal recessive inheritance and the 25% risk of recurrence and was advised about the limitation of prenatal diagnosis by sonographic evaluation in the second trimester.

During the second pregnancy, at 15 weeks of gestation, the fetus was found to have a posterior encephalocele associated with a cerebellar cyst (Figure 1), absent cerebellar vermis (Figure 2), and large and echogenic kidneys (Figure 3). The diagnosis of MKS in the second pregnancy was made based on the sonographic appearance.

Discussion. MKS is characterised by polydactyly, cystic kidneys and a central nervous system malformation (usually a posterior encephalocele). Other associated abnormalities include cleft lip/palate, anophthalmia/microphthalmia, cardiac and genital anomalies, and liver fibrosis. There is both an intra-familial as well as inter-familial variability, the latter, likely the result of genetic heterogeneity. The most striking example of intrafamilial variability is the family reported by Wright et al.: one sib had the classic findings of MKS (posterior encephalocele, polycystic kidneys, post-axial polydactyly); the other had pre-axial polydactyly and a urethral obstruction sequence with no central nervous system anomalies. Dandy-Walker malformation has been observed in siblings of children with the main characteristics of MKS (occipital encephalocele, cystic kidneys, postaxial polydactyly). Other abnormalities reported in MKS include congenital heart disease, and aplasia and abnormal lobulation of the tongue. Facial features observed in fetuses and newborns with MKS include sloping forehead, micrognathia, low-set ears, short neck, broad cheeks, hypertelorism, broad and flattened nose, and wide mouth with full lips.

MKS is common in Finland, and in Guajarti Indians, Belgians, and Kuwaiti Bedouins. Two loci have been described for patients with MKS: 17q21q22 in the Finnish population, and 11q13 in a subset of Middle Eastern and northern African families.

Prenatal diagnosis at 13 weeks was possible in an at-risk case by the demonstration of an abnormal anechoic cystic intracranial structure at 10 weeks gestation; and by the demonstration of a skull defect in the occipital area with herniation of the brain and meninges, and abnormally enlarged kidneys at 13 weeks gestation. Prenatally, MKS must be distinguished from hydrocephalus syndrome, trisomy 13,
Smith-Lemli-Opitz syndrome type II, Goldston syndrome, and Majewski type of short-rib polydactyly syndrome. The breadth of the phenotypic spectrum creates problems in genetic counselling and prenatal diagnosis. MKS should be considered in a proband with any of the key features, even in apparent isolation. The efficacy of second and third trimester ultrasound in subsequent pregnancies is limited since the absence of CNS abnormalities, polydactyly, or renal dysplasia is not completely reassuring. In families where linkage to chromosome 17q21q22 has been established, molecular prenatal diagnosis may be possible.

REFERENCES


Figure 2. Coronal sonogram of the fetal head showing the cerebellar cyst, and splaying of the cervical spine.

Figure 3. Coronal sonogram of the fetal abdomen showing bilaterally enlarged and echogenic kidneys.

Figure 4. Coronal sonogram of the fetal abdomen showing bilaterally enlarged and echogenic kidneys.
Acne and Pregnancy

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COMMON MEDICATIONS

Benzoyl Peroxide

Benzoyl peroxide is a topical treatment for acne that has antibacterial effects and induces skin peeling. About 5% of each topical dose is absorbed systemically. There are no animal or human reproductive studies on benzoyl peroxide, and therefore its potential teratogenic risk is undetermined. However, benzoyl peroxide is commonly used, and there are no case reports about benzoyl peroxide and birth defects in the literature. This, combined with its limited absorption, provides some reassurance that the risk of malformations is likely to be low.

Hydrocortisone

Hydrocortisone is a corticosteroid used topically to treat acne and other dermatologic conditions. There have been no reproductive studies on topical exposures to hydrocortisone specifically, and as such its risk in pregnancy is undetermined.

A literature review of oral cortisol exposures during pregnancy did not find an increased risk for malformations in the exposed group, but it did reveal that the exposed group had an increased risk for prematurity and other complications for the mother and fetus.1 The oral doses in the studies reviewed were presumably much larger than a dose from a topical exposure.

Fraser et al. surveyed 468 women exposed to all corticosteroids in general, and noted no significant increase in birth defects.2 However, in this study, the number of observed cases of cleft palate was different from the expected number (2 vs. 0.2). Because an increase in clefting has been observed in mice exposed to corticosteroids,3 this finding is potentially concerning. Other published studies of oral and inhaled corticosteroids have not reported a significant increase in birth defects in general, or in clefts specifically.4,5,6,7

In summary, although there is a potential connection between oral corticosteroids and cleft palate identified in the human and animal studies, it is unlikely that a topical exposure to hydrocortisone significantly increases the risk of birth defects, including oral clefts.2,3

Salicylic Acid

Salicylic acid is used to treat acne, warts and other dermatological problems. There are no studies specifically evaluate the fetal effects of topical salicylic acid in pregnancy. Oral salicylic acid (aspirin) has not been associated with an increase in malformations when used during the first trimester, but use late in pregnancy has been associated with bleeding, especially intracranial bleeding.8 The risks of aspirin late in pregnancy are probably not relevant for a topical exposure to salicylic acid, even if used late in pregnancy, because its systemic absorption is low. Topical salicylic acid is common in many over-the-counter dermatological agents, and the lack of adverse reports suggests a low teratogenic potential.

ANTIBIOTICS/ANTI-INFECTIVES

Erythromycin

Erythromycin is an antibiotic that is commonly prescribed in pregnancy. Although often taken orally to treat infection, it is also used topically for acne. Erythromycin crosses the placenta minimally; the fetal blood concentration is only 2% to 10% of the maternal serum concentration, and the medication is quickly metabolized by the body.

Takaya et al. found no increased malformations in mice exposed to 1 to 20 times the human dose.9 Human studies on erythromycin have all evaluated oral exposures. Retrospective studies of 79 and 6,972 women exposed in first trimester had no significant increase in birth defects.10,11
Jick et al. examined the prescription records of women exposed to erythromycin during the first trimester and also found no increase in birth defects. Because of these studies and the fact that this medication is commonly prescribed, it is generally assumed that topical erythromycin does not pose a significant increased risk for birth defects.

**Clindamycin**

Clindamycin is an antibiotic related to erythromycin and available both orally and topically for the treatment of acne. It has been studied in both mice and rats at doses up to 180 mg/kg/day without teratogenic effects.

The retrospective Michigan Medicaid study identified 647 women exposed to clindamycin in the first trimester (both oral and topical exposures) and did not note an increased risk for major malformations. Furthermore, a study of 104 women exposed to clindamycin in the second and third trimesters did not suggest an increased risk for prematurity or placental complications. This medication is unlikely to significantly increase the risk for birth defects in either its oral or topical form.

**Tetracycline**

Tetracycline is an antibiotic taken orally to treat acne. This medication belongs to a family of antibiotics that includes minocycline and doxycycline. The half-life of tetracycline is 11-22 hours, so most of the medication is removed from the body in 5 days.

Two retrospective studies found no increase in the incidence of major malformations when women were exposed to tetracycline in the first trimester. However, discoloration of deciduous teeth and the crowns of permanent teeth was seen in children who were exposed to tetracycline after the fourth month of gestation. Studies performed by Cohlan et al., Kline et al., and Kutscher et al. established that infants exposed to tetracycline in utero after the fourth month of gestation may have discoloration of deciduous teeth ('baby teeth'), cavities, and enamel hypoplasia in their teeth. It is believed that tetracycline causes dental discoloration and bone depression because it acts on the calcification process in development. The critical period for calcification begins at four months' gestation and ends twelve months post-partum. Therefore, tetracycline should be avoided after the sixteenth week of gestation and throughout lactation.

The degree of dental staining appears to be proportional to the dose of the medication. Cohlan et al. also found that tetracycline caused long bone growth depression of 40% which normalized when the use of the medication was suspended.

Doxycycline and minocycline, two medications structurally-related to tetracycline, are also used to treat acne. These medications have not been as well-studied as tetracycline; it is, however, generally assumed that doxycycline and minocycline similarly affect the fetal calcification process. Therefore, these medications should also be avoided after the first trimester of pregnancy through the breastfeeding period.

**Sodium Sulfacetamide**

Sodium sulfacetamide is a topical anti-infective medication used to treat acne and seborrheic skin conditions. It belongs to the class of medications termed sulfonamides, and most reproductive studies examine sulfonamides as a class and in oral dosages, making it difficult to extrapolate the potential risk for a topical medication such as sulfacetamide.

The maternal use of sulfonamides near delivery can lead to newborn toxicity, resulting in anemia and jaundice and, theoretically, kernicterus, although this has yet to be documented in the literature. There have been two large retrospective studies of sulfonamide exposure, which involved 1,445 and 3,465 women exposed in the first trimester; neither study found an increased risk for malformations from the class in general.

In contrast, other case controlled studies raised concerns about sulfonamide use in pregnancy. A 1971 case-control study by Nelson et al. determined the pregnancy exposures of 1,369 patients, 468 of whom...

Continued on page 22
Acne continued from page 21

had babies with congenital malformations. They observed that significantly more mothers of the babies with birth defects took sulfonamides than the control mothers. Saxon et al. retrospectively evaluated 599 children who were born with oral clefts. The mothers of children with malformations in addition to the oral clefts were more likely to have taken sulfonamides than mothers of children with isolated oral clefts.

Because topical sulfacetamide has never been specifically studied to determine its potential teratogenic risk, one cannot definitively conclude that it does not cause birth defects. However, because it is topical and, for the most part, sulfonamides as a class do not appear to significantly increase the risk for birth defects, it is unlikely that topical sulfacetamide causes a significantly increased risk for malformations.

Breastfeeding while using sulfonamides is probably not a risk to a healthy infant. At most 1-2% of a maternal, oral dose of sulfonamides enters the breastmilk. However, sulfonamides can potentially cause anemia and jaundice in stressed, premature or hyperbilirubinemic infants. In addition, if an infant has glucose-6-phosphate-dehydrogenase deficiency, breastfeeding should be avoided while taking sulfonamides, as sulfonamides act as oxidative stressors and can result in a hemolytic crisis.

RETINOIDS

Isotretinoin

Isotretinoin is an oral retinoid used to treat cystic acne. A known teratogen, this medication is contraindicated during pregnancy due to the characteristic malformations it causes. The pattern includes defects of the CNS, thymus, craniofacial and cardiovascular systems, as well as conotruncal malformations.

Isotretinoin is believed to affect initial differentiation and migration of cephalic neural crest cells, and the critical period for this medication is 2 to 5 weeks post-conception. Because the teratogenicity of isotretinoin is well-known, we have chosen to focus upon other common acne medications in this review, rather than summarizing the literature about isotretinoin. Despite the half-life of approximately 1 day (manufacturer insert), due to the teratogenicity of this medication it is recommended that isotretinoin be discontinued at least one month prior to attempting pregnancy.

Tretinoin

Tretinoin is a component of various topical acne creams. Because this medication is related to isotretinoin, there is concern that tretinoin could potentially have similar teratogenic effects on the fetus. Two case reports have described infants born to women using topical tretinoin during the first trimester of pregnancy. The infants had malformations that mimic the birth defects associated with isotretinoin. In contrast, a prospective cohort study failed to find an association between birth defects and 215 women exposed to tretinoin in the first trimester. Shapiro et al. did not observe a significant increase in number of livebirths, spontaneous abortions, infants of low birth weight, major malformations, duration of pregnancy, or Cesarean sections in 94 women exposed to tretinoin versus controls.

A dose-response relationship potentially could play a role in the effects of tretinoin; it is of note that 5-31% of tretinoin is absorbed systemically, depending on whether the skin is healthy or dermatitic. Although prospective studies have shown no increase in congenital anomalies, the case reports and biological plausibility of the anomalies raise concern about this medication. While such risks are likely to be low given the low topical absorption, health professionals should encourage women to weigh the risk and benefits of tretinoin during pregnancy.

Adapalene

Adapalene is a retinoid used in a topical gel form for the treatment of acne. As such, there are theoretical risks for retinoid embryopathy. However, the manufacturer reports that only trace amounts of adapalene are absorbed from the skin (trace is defined as less than 0.25 ng/ml). The manufacturer’s studies on pregnant rats and rabbits using doses 120 to 150 times the maximum human topical dose did not show an increased risk of adverse outcome or malformations.
There has been one human case report of adapalene use during weeks 4-13 of pregnancy; the fetus had intra-uterine growth retardation, anophthalmia and agenesis of the optic chiasm, and the pregnancy was aborted at 13 weeks. The anomalies seen in this pregnancy are not typical of those seen with other retinoid exposures. In addition, as with any case report, the malformations could be coincidental and unrelated to the adapalene. There have not been any other human studies or case reports to date. The overall risk of adapalene is undetermined because there have not been any human studies. However, because only trace amounts of the gel are absorbed into the skin, it is unlikely that doses large enough to induce malformations could reach a fetus.

OTHER MEDICATIONS

Azelaic Acid

Azelaic acid is a topical cream for acne. The manufacturer’s studies in animals do not show an increase in malformations at doses much higher than the maximum human dose. There have not been any human reproductive studies to date.

While it is reassuring that animal studies do not show teratogenicity and that the fetal dose is small because the medication is topical, the risk of azelaic acid is undetermined because there have been no human studies.

CONCLUSIONS/SUMMARY

In summary, acne medications present a range of risks during pregnancy. Because of its proven teratogenicity, it is well known that isotretinoin should not be taken during pregnancy. Additionally, tetracycline and its derivatives should not be used after 16 weeks gestation due to its effects on calcium-containing tissue, particularly teeth. The risks of other medications such as tretinoin are less certain, while some commonly used medications, like benzoyl peroxide, do not appear to pose a significant risk for malformations.

Because of the widely known teratogenic effects of isotretinoin, many women are wary of acne medications in general during pregnancy. However, there are a wide variety of medications available for the treatment of acne, many of which pose a minimal risk if applied topically during pregnancy.

An unedited version of review is also posted as ITIS Newsletter Vol.7 No.5, February 2000, on the Illinois TIS website - http://www.fetal-exposure.nwu.edu

REFERENCES


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