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Does it matter if I'm 'just' pregnant?

Background

The time before a woman has confirmed her pregnancy is an important time for both the woman and her unborn baby's wellbeing. With the period of organogenesis largely occurring between the third and eighth week of development, early pregnancy is a time when a woman may have problems related to the pregnancy itself, or where diseases have a higher risk of morbidity in the woman or the fetus. Yet, the woman and her doctor, may be unaware of the pregnancy.

Objective

This article outlines presenting complaints where a doctor should specifically explore the possibility of early pregnancy in a woman in her reproductive years, as pregnancy may have an impact on the management, and ultimately the wellbeing, of both the woman and the fetus.

Discussion

Identification and appropriate management of the coexisting pregnancy and presenting condition allows the general practitioner to provide the most appropriate care in this clinical situation.

Keywords: pregnancy; pregnancy complications; teratogens



This article considers the first few weeks after conception when the possibility of early pregnancy has implications on the differential diagnosis and management of a range of issues with which a woman may present. This article explores some of the issues the general practitioner should consider if a woman in her reproductive years presents with:

- a potential problem of early pregnancy
- a medical problem that may be managed differently in early pregnancy
- an exposure that takes on a different significance in early pregnancy.

Most women experience some pregnancy signs or symptoms as early as 3 weeks after conception, with amenorrhoea being the cardinal early pregnancy sign. However, as many women have irregular bleeding patterns or an occasional prolonged menstrual cycle, it can be difficult to establish amenorrhoea in early pregnancy.¹ Associated common symptoms of early pregnancy are nausea (with or without vomiting), breast tenderness, increased frequency of urination, and fatigue. Other symptoms include food cravings and aversions, mood changes, light headedness, abdominal bloating, constipation, heartburn, low back pain, nasal congestion, and uterine cramps similar to those felt before or during menses. Most of these symptoms can be attributed to the changing hormonal milieu of pregnancy.²

However, at this early stage of pregnancy, neither symptoms nor physical examination are sensitive for pregnancy diagnosis. The diagnosis of early pregnancy confirmed by laboratory detection of human chorionic gonadotropin (HCG). If pregnancy has occurred, HCG can be detected in serum and urine as early as 8 days after the luteinising hormone surge. However, this varies as urine tests have differing sensitivities with some set to a pregnancy HCG range of over 7 or 8 weeks.³

Potential problems of early pregnancy

Irregular bleeding

'My periods seem all over the place'

Vaginal bleeding is common in the first trimester of pregnancy, occurring in 20–40% of pregnant women.⁴ It may be light or heavy,



intermittent or constant, painless or painful. Women presenting with irregular vaginal bleeding are less likely to consider pregnancy, but pregnancy must be considered as this may indicate a serious problem.

The four major sources of vaginal bleeding in early pregnancy are:

- ectopic pregnancy
- miscarriage – either threatened or impending
- implantation of the pregnancy
- cervical, vaginal, or uterine pathology (eg. polyps, inflammation).

Table 1. More about ectopic pregnancy

The classic symptoms of ectopic pregnancy are: abdominal pain, amenorrhoea, vaginal bleeding⁴³

These symptoms can occur in both ruptured and unruptured cases and the patient may present with any combination⁴⁴

Approximately 1 in 50 pregnancies are ectopic and the prevalence of ectopic pregnancy among women presenting to an emergency department with first trimester bleeding, pain, or both ranging from 6–16%.^{45,46} Overall, the incidence of ectopic pregnancy is increasing in association with an increased incidence of pelvic inflammatory disease; a major risk factor. Other risk factors include a history of tubal disease, previous ectopic pregnancy, tubal surgery, previous genital infection, and pregnancy derived from in vitro fertilisation.⁴⁷ Intrauterine contraceptive devices (IUD) lower the overall risk of both ectopic and intrauterine pregnancy, however, if a woman using an IUD becomes pregnant, she is at a higher risk of ectopic pregnancy⁴⁵

It is crucial to diagnose early, as detection before tubal rupture decreases maternal morbidity and mortality and enhances greater treatment options

Transvaginal ultrasonography is recommended in women presenting with pain or bleeding with a positive pregnancy test in whom an intrauterine pregnancy has not been previously confirmed. Ultrasound examination can determine whether the pregnancy is intrauterine or extrauterine (ectopic) and, if intrauterine, whether viable (fetal cardiac activity present) or unviable. If more than 6 weeks have lapsed since the first day of the woman's last menstrual period, the absence of an intrauterine gestational sac is highly suggestive of ectopic pregnancy. However, at earlier gestation a pregnancy that may be intrauterine may not yet be identifiable by ultrasound

On transvaginal ultrasound, an intrauterine sac is likely to be visible when HCG >1500 IU/L and fetal heartbeat likely to be detectable when HCG >10 000 IU/L. HCG usually doubles every 48 hours in early pregnancy and serial HCG monitoring can be helpful for assessment in early pregnancy. A sustained fall suggests miscarriage, a plateau or slow rise or fall suggests miscarriage or ectopic pregnancy and fluctuating levels are highly suggestive of ectopic pregnancy. However, normal HCG levels and doubling does not exclude ectopic pregnancy or miscarriage and HCG levels must be considered together with the clinical picture^{48,49}

The exact aetiology of bleeding in the first trimester often cannot be determined and the initial goal is to confirm or exclude pregnancy. If the woman is pregnant, then the GP needs to make a definitive diagnosis of the cause of bleeding when possible, and exclude the presence of an ectopic pregnancy in other cases, as it is the leading cause of maternal death in the first trimester of pregnancy⁵ (Table 1). Although significant pelvic pain or cramping makes miscarriage and ectopic pregnancy more likely, it is important to remember that light, intermittent, painless bleeding can also result from an ectopic pregnancy.

Abdominal pain

'My period pain is much worse than usual'

Abdominal pain may well be 'just period pain', however in any woman of reproductive age presenting with abdominal pain, a pregnancy related cause of the pain needs to be considered. These causes include ectopic pregnancy and threatened or actual miscarriage (Table 2).

Diseases more likely in early pregnancy

'My left calf hurts'

There are a number of diseases that may be 'unmasked' or have a higher incidence due to the physiological changes of early pregnancy. As a consequence, the confirmation of a pregnancy may alter the likely differential diagnosis of the presenting symptoms. These include urinary tract infections, thyroid disease, cardiovascular disease and thromboembolic disease, with pulmonary embolism increasing 5–6 fold during pregnancy due to changes in the profile of clotting factors and a predisposition to venous stasis.

Unwanted pregnancy

For some women, the pregnancy may be unwanted, therefore it may be the pregnancy itself that is of most concern. These women may need time to consider the issues around an unwanted pregnancy in order to make the decision that is best for them. If the woman chooses

Table 2. More about threatened miscarriage

Uterine bleeding in the presence of a closed cervix and sonographic visualisation of an intrauterine pregnancy with detectable fetal cardiac activity is diagnostic of threatened miscarriage. 'Threatened' is used to describe these cases as miscarriage does not always follow uterine bleeding in early pregnancy; 90–96% of pregnancies with both fetal cardiac activity and vaginal bleeding at 7–11 weeks gestation do not miscarry, even in the setting of heavy or repeated bleeding^{50,51}

As miscarriage and ectopic pregnancy are first trimester indications for the use of RhD immunoglobulin (anti-D) in women who are rhesus negative without preformed anti-D antibodies, blood group and antibodies should also be checked. There is currently insufficient evidence to support the use of RhD immunoglobulin in a threatened miscarriage before 12 weeks⁵²



to terminate the pregnancy, the options available depend on the pregnancy gestation (eg. early medical abortion with mifepristone is increasingly available). Early diagnosis of pregnancy gives the greatest opportunity for appropriate counselling and the most options.

Medical problems managed differently in early pregnancy

There are a number of maternal illnesses that have different implications in pregnancy, either because the disease results in greater maternal morbidity, the disease has implications on the fetus, or because management differs in pregnancy. It is important to identify these early, as there may be an opportunity for interventions that minimise the risk of adverse outcomes.⁶

Diseases with greater morbidity in pregnancy

'Does it matter if these symptoms are the flu/chicken pox?'

A number of diseases are known to have greater maternal morbidity in pregnancy. This was seen in the H1N1 influenza A 2009 (swine flu) pandemic where pregnant women had disproportionately high morbidity and mortality rates⁷ and were therefore routinely offered antivirals.

This increased complication rate is also seen when women contract varicella in pregnancy. Along with the potential teratogenic effect on the fetus, varicella pneumonia is more common and may be more severe in pregnancy,⁸ with a mortality rate in untreated pregnant women of over 40%, which is decreased markedly by prompt supportive care and antivirals.⁹

'If I am pregnant, does it matter that much about my blood sugar?'

There are a number of maternal diseases that have potential effects on the fetus (and mother). This may be a result of the condition itself, the medicine used, or a genetic predisposition associated with both the disease and fetal outcomes. Consequently, if a woman is diagnosed with one of these conditions, or presents for ongoing management, the identification of early pregnancy is crucial as management may be altered. For pre-existing maternal conditions this process is ideally initiated before pregnancy.

Diabetes

The increased risk of fetal and pregnancy complications in women with pregestational diabetes is well established, with increases in congenital malformations, perinatal mortality, macrosomia, caesarean delivery, preterm delivery, pre-eclampsia, neonatal jaundice and respiratory distress syndrome.¹⁰ Poorer metabolic control is associated with a higher risk of these adverse outcomes, with repeated observations that normalising blood glucose concentrations before and early in pregnancy can reduce risk to nearly that of women without diabetes.^{11–13} Therefore, GPs have a crucial role in assisting women with diabetes, before and early in their pregnancy, to achieve optimal metabolic management.

Asthma

Asthma is the most common medical condition encountered during pregnancy, occurring in 3–8% of women. It may improve, worsen, or remain unchanged during pregnancy. It may affect the outcome of pregnancy, with a small but significant increase in pregnancy complications, including a 15–20% increased risk of perinatal mortality, pre-eclampsia, preterm delivery and low birth weight infants compared to women without asthma. For women with more severe asthma, this increase is higher. There are no known increased risks of congenital malformations.^{14,15} The primary goals of asthma management of acute episode prevention and ongoing pulmonary function optimisation remain unchanged in pregnancy and serve to maximise both maternal and fetal health.¹⁶ Experience with many of the medications used to treat asthma suggest minimal risk for use during pregnancy.¹⁷

Hypothyroidism

Adequate thyroid hormone is essential for normal development of the fetal brain. If a fetus is not exposed to enough thyroid hormone, it may have permanent neuropsychological and cognitive impairment. Hypothyroidism can also result in low birth weight, pre-eclampsia, placental abruption, preterm delivery, increased perinatal morbidity and mortality and postpartum haemorrhage.¹⁸ Women normally increase production of thyroid hormone during pregnancy. However, unlike euthyroid women, women with hypothyroidism are unable to increase thyroidal T4 and T3 secretion.¹⁹ Therefore greater monitoring is required in pregnancy with approximately 75–85% of women with pre-existing hypothyroidism requiring more thyroxine replacement.²⁰

Epilepsy

Maternal epilepsy is associated with a 2–3 fold increase in the incidence of congenital malformations if treated with antiepileptic drugs (AED). This is especially so in the context of higher dosage and polytherapy, with some medicines such as valproic acid thought to particularly contribute, but malformations are increased even without drug treatment.²¹ A pregnant woman with epilepsy requires careful reappraisal of her epilepsy management. In established pregnancy, changes to alternate AED therapy should not be undertaken solely to reduce teratogenic risk. Changing AEDs may precipitate seizures, overlapping AEDs during a changeover exposes the fetus to effects of an additional AED and there is limited advantage to changing AEDs if pregnancy has been established for several weeks.²² However, optimisation of the dosage and monitoring of plasma levels, the pre-pregnancy prescription of 5 mg of folic acid (as low serum folate levels in women with epilepsy are independently associated with an increased risk of major fetal malformations),²³ and the importance of adequate sleep, medical compliance, and minimising stress and other factors known to precipitate seizures needs to be reinforced.

Urinary tract infection

Bacteriuria occurs in 2–7% of pregnancies, often developing in the first month. It is associated with an increased risk of preterm birth, low birth



weight and perinatal mortality,^{24,25} with treatment of asymptomatic bacteriuria during pregnancy reducing these complications.²⁶

Urinary tract infection (UTI) and bacteriuria have a greater morbidity in pregnancy. The smooth muscle relaxation and subsequent ureteral dilatation that accompany pregnancy are thought to facilitate the ascent of bacteria from the bladder to the kidney. Consequently, bacteriuria during pregnancy has a greater propensity to progress to pyelonephritis (up to 40%),²⁷ requiring greater vigilance to manage and establish the adequacy of treatment.

Hereditary conditions

'Does it matter that my nephew has just been diagnosed as having Fragile X syndrome/cystic fibrosis?'

The possibility of an inheritable disease requires counselling and testing. This may take several months as the process may include both patient and partner testing for carrier status, determination of the particular genetic alteration, and subsequent testing of the fetus. Ideally testing occurs before pregnancy. However, if either parent potentially has a pre-existing hereditary condition, or one is discovered that may affect a fetus and she is pregnant, time is of the essence.

Exposures that have a different significance in early pregnancy

Teratogens are agents that can disturb the development of an embryo or fetus and these are important in early pregnancy (*Table 3*).

During the period of fetal organogenesis (weeks 3 to 8 of the pregnancy), the embryo is particularly sensitive to teratogenic insults with exposure potentially producing cell death or altering normal growth of tissues or cells. The consequences of these include miscarriage, stillbirth or infant death, low birth weight, congenital malformations, cognitive changes, developmental delays and childhood cancers.

Exposure to infections

'My neighbour's daughter has a rash and I've been looking after her. Does it matter if I happen to be pregnant?'

Exposure to a number of infections can cause teratogenic effects in the fetus. The original concept of the 'TORCH' perinatal infections acronym was to group five infections with similar presentations, including rash and ocular findings.²⁸ These five infections are toxoplasmosis, other (syphilis), rubella, cytomegalovirus (CMV) and herpes simplex virus (HSV). The most relevant of these in early pregnancy is exposure to toxoplasmosis, rubella and CMV. Since the original TORCH concept, a number of other infections are now known to be potentially teratogenic to the fetus. These include human immunodeficiency virus (HIV), varicella, human parvovirus, *Listeria monocytogenes* and Brucellosis.

As a result of a wide range of often nonspecific clinical presentations and difficulty in interpreting laboratory findings, all of these infections can be difficult to recognise and diagnose and require a high index of alertness for both pregnancy and exposure.^{29,30}

Exposure to a potentially infectious teratogen should lead to confirmation of pregnancy and, if possible, the subsequent identification of the infectious agent of exposure and the woman's immunity to it. In the pregnant woman without adequate immunity, timely counselling and possibly further investigations, and occasionally the use of immunoglobulin, should be considered.

Exposure to medicines

'If I'm pregnant should I stop taking my antidepressants?'

Much of the information regarding the safe use of medicines during pregnancy was obtained decades ago, before pregnant women were excluded from drug studies because of concerns about risks to the fetus. As such, there is limited information on the safety of most medicines and vaccinations in pregnancy and even more limited information on the safety of over-the-counter, herbal and homeopathic medicines.

Exposure to medicines in pregnancy is based on an assessment of:

- a risk-benefit analysis, balancing the risks and benefits to the woman and fetus of starting or continuing a medicine versus not using or stopping it
- determining the most appropriate medicine and the minimum dose required for appropriate management³¹
- any special or enhanced monitoring required in pregnancy (eg. lithium or thyroxine)
- any other management required to mitigate the use of a medicine (eg. the prescription of increased folate with antiepileptic drug use).

Exposure to cigarettes, alcohol and other substances

'Does it matter if I'm just pregnant and I smoke or drink? I'll stop later if I am'

Smoking during pregnancy is the most important modifiable risk factor associated with adverse pregnancy outcomes.³² It is associated with 5% of infant deaths, 10% of preterm births, and 30% of small-for-gestational-age infants.³³ Smoking also increases the risk of placental abruption, preterm premature rupture of membranes and placenta previa. Its effects are probably from multiple causes and may include chromosomal problems and direct toxicity as a result of exposure to the over 4000 chemicals in typical tobacco smoke.³⁴ Therefore, any exposure at any stage of pregnancy is potentially detrimental.

With regards to alcohol, fetal alcohol spectrum disorder describes a broad range of adverse sequelae in alcohol exposed fetuses with a continuum of outcomes associated with fetal exposure to alcohol, and negative effects seen throughout pregnancy.³⁵ There is no exact dose response relationship between the amount of alcohol consumed during pregnancy and fetal effects, with not drinking being the safest option in pregnancy.³⁶ In addition, all illicit drugs are associated with some degree of adverse effect and should not be taken in pregnancy.³⁷

Pregnant women are typically highly motivated to modify their behaviour³⁸ and GPs are in an ideal position to harness this motivation in their counselling and management of women who use cigarettes, alcohol and drugs.³⁹



Exposure to physical agents, metals, chemicals and solvents

'If I'm pregnant does it matter if I have this chest X-ray you ordered?'

Exposure to a number of physical agents, metals, chemicals and solvents can cause teratogenic effects in the fetus. For women with such potential exposures it is important to establish pregnancy and then mitigate for this exposure. However, only a small proportion of the several thousand exposures have been adequately assessed for effects on the fetus, and as such, all exposures should be considered in a prudent fashion. Chemical and physical agents that are reproductive hazards for women in the workplace are considered in *Table 3*.

Exposure to extreme heat

'Does it matter if I get a fever with this cold if I'm pregnant?'

The human fetus' temperature is about 1°C higher than the maternal temperature. Animal studies suggest that perinatal risks such as neural defects increase with maternal heat exposure. Similar findings were found in human studies related to febrile illnesses, sauna use, and hot tub use.^{40,41} Therefore in early pregnancy, the use of a suitable antipyretic such as paracetamol is recommended, although with disease specific management.

Summary

Early pregnancy is a crucial time in a woman and her unborn baby's wellbeing. Particular situations where a doctor should specifically explore if a woman in her reproductive years is pregnant are when:

- a presenting complaint may be related to a complication of the pregnancy itself (eg. when a woman presents with abdominal pain or irregular vaginal bleeding). In these cases, even without a history of amenorrhoea, the GP should routinely consider both pregnancy

and nonpregnancy related problems. The most important of these is ectopic pregnancy

- a differential diagnosis would be altered by the confirmation of pregnancy
- management of a disease would be altered in the context of pregnancy, such as if the disease has a greater impact on the mother or fetus (eg. varicella or influenza)
- management of an ongoing disease would be altered by the existence of pregnancy. This includes modification of monitoring and medication use (eg. in women with pre-existing diabetes, thyroid disease and epilepsy)
- a potentially inheritable condition has been identified in either parent
- the woman has been exposed to an agent that may have implications to the fetus.

In all of the above, in order to achieve optimal outcomes for both the woman and her baby, a GP's management may change with the knowledge of early pregnancy. As such, the possibility of pregnancy should be explored.

Author

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Table 3. Chemical and physical agents that are reproductive hazards for women in the workplace⁴²

Agent	Observed effects	Potentially exposed workers
Cancer treatment drugs (eg. methotrexate)	Infertility, miscarriage, birth defects, low birth weight	Healthcare workers, pharmacists
Certain ethylene glycol ethers, eg. 2-ethoxyethanol (2EE) and 2-methoxyethanol (2ME)	Miscarriage	Electronic and semiconductor workers
Carbon disulfide (CS ₂)	Menstrual cycle changes	Viscose rayon workers
Lead	Infertility, miscarriage, low birth weight, developmental disorders	Battery makers, solderers, welders, radiator repairers, bridge painters, firing range workers, home remodelers
Ionizing radiation (eg. X-rays and gamma rays)	Infertility, miscarriage, birth defects, low birth weight, developmental disorders, childhood cancers	Healthcare workers, dental personnel, atomic workers
Strenuous physical labour (eg. prolonged standing, heavy lifting)	Miscarriage, premature delivery	Affects many types of workers



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