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Fish Parasites: A Growing Concern During Pregnancy

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Intestinal parasitic worms affect more than 2 billion people worldwide according to the World Health Organization. Fish-borne parasitic infections are becoming more common with the increasing popularity of sushi, sashimi, Carpaccio, tartare, gefilte, and ceviche. The ingestion of these parasites can cause severe anemia, malabsorption, severe abdominal pain, nausea, vomiting, strong allergic reactions, and gastric ulcers. Knowledge about fish parasites and pregnancy is limited.

A literature search on PubMed and Web of Science used the search terms “fish parasites” OR “diphyllobothrium” OR “anisakiasis” OR “pseudoterranova” OR (“food borne parasites” AND “fish”) AND “pregnancy” OR “maternal” OR “fetus” OR “fetal” OR “newborn” OR “neonatal” OR “childbirth.” No limit was put on the number of years searched.

There were 281 publications identified. The abstracts of all of these publications were read. After exclusion of the articles that were not relevant to pregnancy, pregnancy outcome, and fish parasites, there were 24 articles that became the basis of this review. The pathophysiology, altered maternal immunity related to the infection, limited information about fish-borne parasitic infections and pregnancy, and treatments are discussed.

The main impact of a fish-borne parasitic infection on pregnant women is anemia and altered immunity, which may increase the risk of a maternal infection. The primary fetal effects include intrauterine growth restriction and preterm delivery.

Target Audience: Obstetricians and gynecologists, family physicians.

Learning Objectives: After completing this activity, the learner should be better able to recognize the global impact of intestinal parasitic worm infections; identify the 3 fish-borne parasites that affect humans; understand the immunologic response of a pregnant patient to an invading parasite; summarize the current treatment for the fish parasites.

According to the World Health Organization (WHO), more than 2 billion people worldwide are affected by intestinal parasitic worm infections.¹ These infections are primarily found in underdeveloped and developing countries where the majority of people live in the lower tiers of the socioeconomic classes.^{1,2} The

greatest numbers of affected individuals are in sub-Saharan Africa, the Americas, Europe, China, and East Asia.^{1,3} In addition, the WHO estimates more than 250 million preschool-age children and more than 600 million school-age children from 70 different countries are currently infected with intestinal parasitic infections and are in need of treatment.¹

The growing international markets' importation of foods, availability of international travel, and ever expanding movement of populations increase the risk of exposure and infections of populations all over the world.⁴ Most markets are accustomed to recognizing and dealing with meat-borne infectious diseases of

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animals that can be transmitted to humans (zoonotic infections); however, little is known about fish-borne parasitic zoonoses. The fish-borne zoonotic infections are currently listed within the group of neglected tropical diseases responsible for more than 800 million infections worldwide in 2012.² The current cultural trend toward modern food choices, such as sushi, sashimi Carpaccio, tartare, gefilte, and ceviche, leads to the ever increasing exposure of infection. Furthermore, many Americans who eat fish at home may not properly prepare the fish or may undercook it, which allows the parasite to survive and be ingested. These parasites when ingested can cause mild to severe anemia, malabsorption, severe abdominal pain, nausea, vomiting, strong allergic reactions, and gastric ulcers.⁵

Women are often disproportionately affected by food-borne parasites because of normative societal roles of food preparation and handling, child care, and housework; this is especially true in third-world countries. A major concern arises when women are pregnant and become infected with fish parasites. The burden of infection differs with each woman, as does the impact on the pregnancy. In some areas of the world, as many as 90% of pregnant women are infected with some form of a parasitic infection. In the United States, the incidence of infection is estimated to be 22 per 10,000 pregnancies.⁶ Many infected women, at the time of diagnosis, are found to have more than 1 parasite, therefore increasing parasitic burden and complications. Questions arise about the overall effect of the parasitic burden and specifically fish parasites on the pregnant woman and her fetus. Collectively, these effects may range from anemia to more severe consequences such as infestation of the placental bed and amniotic fluid, which could lead to an increased risk of maternal morbidity/mortality.

Although there is information available about parasitic infections and pregnancy, knowledge about fish parasites and pregnancy is limited. The purpose of this article is to review what is currently known about maternal infections with fish parasites and the impact of these infections on pregnancy and pregnancy outcomes.

METHODS

A literature search by a reference librarian was undertaken using the search engines PubMed and Web of Science and using the search terms “fish parasites” OR “diphyllobothrium” OR “anisakiasis” OR “pseudoterranova” OR (“food borne parasites” AND “fish”) AND “pregnancy” OR “maternal” OR “fetus” OR “fetal” OR “newborn” OR “neonatal” OR “childbirth.” No limit was put on the number of years searched. There

were 281 publications identified. The abstracts of all the articles were read, and full articles corresponding to fish parasites and pregnancy were then examined. Lastly, the references for all of the articles linking fish parasites and pregnancy or pregnancy outcomes were screened for any additional applicable articles. There were 70 abstracts identified, of which 5 of the abstracts were duplicates. Another 7 articles were added after screening the reference list of each of the identified articles for additional publications. After exclusion of irrelevant articles, there were 24 articles that became the basis of this review (Fig. 1) (Table 1).

Pathophysiology of Fish Tapeworms

Collectively, the fish tapeworms that are linked with human infestation are *Diphyllobothrium latum*, *Pseudoterranova decipiens*, and *Anisakis simplex*. *Diphyllobothrium latum* “fish tapeworm” is part of the family *Diphyllobothrium* that consist of more than 50 species.⁵ This parasitic tapeworm is responsible for most reported parasitic flatworm infections in humans. It is most commonly acquired in populations where the act of eating fresh, raw, or undercooked food is commonly done. The more diverse the eating habits of a society become, the more likely the population will become infected. The life cycle of the worm starts with expulsion of the eggs into a water source. The egg then hatches, becoming a motile embryo waiting to be ingested by a crustacean and entering its first larval stage, called a proceroid. Once the crustacean is eaten, the worm begins its second stage, plerocercoid. After the second stage host is consumed by the final host, the plerocercoid becomes the sparganum, rapidly developing into a mature worm. The tapeworm can grow as long as 2 to 15 m, with both male and female segments, and

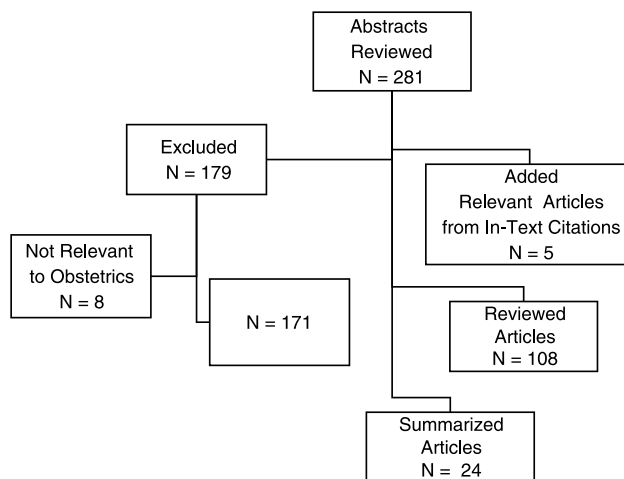


FIG. 1. Flow diagram.

TABLE 1
Articles Evaluated

Authors	Title	Study Type	Purpose
Urassa et al ⁷	Effectiveness of routine anthelmintic treatment on anaemia in pregnancy in Rufiji District, Tanzania	Cluster randomized controlled trial	Assess the effectiveness of anthelmintic treatments in pregnancy
Oppenheimer ⁸	Iron-deficiency anemia: reexamining the nature and magnitude of the public health problem	Meta-analysis	Examine the relationship between iron and effects on parasitic infections
Dent ⁹	For better or worse: common determinants influencing health and disease in parasitic infections, asthma and reproductive biology	Review of literature	Immunological response to infection
Arizono et al ¹⁰	Diphyllobothriasis associated with eating raw Pacific salmon	Review of literature	Diphyllobothrium infected salmon and human infection
Cabello ⁴	Salmon aquaculture and transmission of the fish tapeworm	Review of literature	Examine the transmission of <i>Diphyllobothrium</i> between wild and caged salmon
Chai et al ⁵	Fish-borne parasitic zoonoses: status and issues	Review of literature	Overview of fish-borne parasitic infections
Cooper ¹¹	The potential impact of early exposure to geohelminth infections on the development of atopy	Clinical review	Effect of helminth infections on the immune system
Elliott et al ¹²	The impact of helminthes on the response to immunization and on the incidence of infection and disease in childhood in Uganda	Randomized double blind, placebo-controlled	To determine the effects of helminths and their treatment in pregnancy and in young children on immunological and disease outcomes in childhood.
Galan-Puchades et al ¹³	Human <i>Bertiella stuederi</i> in Spain, probably of African origin	Case report	Gravid woman infected with <i>Bertiella stuederi</i>
van Hooijdonk et al ¹⁴	In vivo antimicrobial and antiviral activity of components in bovine milk and colostrum involved in non-specific defence	Review of literature	Assess several components of bovine milk in defense against infection via modulation of the immune system
Klikhs ¹⁵	Anisakiasis in the Western United States: four new case reports from California	Case series	Reviewing four cases involving anisakiasis
Leder and Weller ¹⁶	Intestinal tapeworms	Review of literature	Overview of intestinal parasitic worms
McClelland ¹⁷	The trouble with sealworms: a review	Review of literature	Overview of <i>P. decipiens</i> species complex
Mercado et al ¹⁸	Human infection by <i>P. decipiens</i> in Chile: Report of 7 cases	Case series	Review of 7 cases of nematode Anisakidae
McClure et al ¹⁹	The association of Parasitic Infections in Pregnancy and maternal and fetal anemia: A cohort study in coastal Kenya	Cohort study	To determine the impact of helminthes and malaria on maternal anemia
Muthayya et al ²⁰	Low maternal vitamin B ₁₂ status is associated with intrauterine growth retardation in urban South Indians	Prospective Cohort	To assess dietary, micronutrient status in healthy pregnant women the association with IUGR
Oppenheimer ⁸	Iron-deficiency anemia: reexamining the nature and magnitude of the public health problem	Literature review	To show a relationship between iron deficiency and infectious morbidity.
Scholz et al ³	Update on the human broad tapeworm (genus <i>Diphyllobothrium</i>), including clinical relevance	Review of literature	Overview and clinical impact of all tapeworm
Tietze and Jones ⁶	Parasites during pregnancy	Review of literature	Overview of parasitic infection in pregnancy
Trussell and Beeley ²¹	Infestations	Review of literature	Summarization of treatments
Yu et al ²²	A human case of gastric infection by <i>P. decipiens</i> larva	Case report	Specific parasitic infection and its impact on a patient
Urassa et al ⁷	Effectiveness of routine anthelmintic treatments on anemia in pregnancy in Rufiji District, Tanzania	A cluster randomized controlled trial	Anemia and treatment and its effects on pregnancy
Abrahams ²³	Immunology of the maternal-fetal interface	Review of literature	Clarification of the immunological relationship between mother and fetus

(Continued on next page)

TABLE 1. (Continued)

Authors	Title	Study Type	Purpose
Vargas-Villavicencio et al ²⁴	Immunoendocrine mechanisms associated with resistance or susceptibility to parasitic disease during pregnancy	Literature review	Relationship between the immune and endocrine systems
WHO Media Centre ¹	Soil-transmitted helminthes infections	Literature review	Updating medical professionals
WHO new release ²	WHO urges governments to increase investments to tackle neglected tropical disease	Literature review	Updating medical professionals

can live up to 10 years within its host, producing millions of eggs.⁵

Globally, in the early 1970s, the incidence of *Diphyllbothrium* was estimated at 9 million cases and, most recently, has been estimated at approximately 20 million cases worldwide, with the most common infections occurring in North America, South America (Chile, Peru, and Argentina), as well as Asia, and most of Europe and Russia.^{3,4} The overall incidence in both Europe and North America are severely underreported; however, as the rate of international travel has steadily increased, the reported infection rate has also steadily increased.^{1,2} Recently, a dramatic increase in the prevalence of *Diphyllbothrium* was observed in Brazil from salmon transported from the aquaculture industry in southern Chile.⁴ This well-established market practice resulted in several severe outbreaks in the Brazilian population, and now many local lakes are grossly contaminated. A second study completed by Arizono et al¹⁰ revealed a 27% increased rate of infection with salmon harvested off the coastal waters of Japan. Infections with this type of parasite are generally thought to produce a mild illness. However, in cases of severe parasitic burden, it can result in severe anemia and small bowel obstruction.⁵

Pseudoterranova decipiens belongs to the *Pseudoterranova* species complex commonly known as the “sushi worm,” “seal worm,” or “cod worm.” This parasite is commonly found in various marine life fishes, which can live in a variety of salinities ranging from fresh, to brackish, to salt water. Infections can range from minor to severe in humans. Infected fish have been identified from regions such as the northern Atlantic, Canadian coast, Japanese waters, and as near as the gulf of Maine.

The life cycle consists of embryo-containing eggs, which are passed in the stool from the contaminated host. The ova make their way to the bottom of the sea bed and go through 2 stages of development. Stage 2 can survive as free-living larva up to 140 days in temperatures between 5°C and 20°C. Stage 2 larva infect crustaceans and mature into stage 3 larva. Upon ingestion of the infected crustacean, the parasite migrates into both the muscle tissues and the gastrointestinal tract of the host within a week of ingestion. The preferred host of the fish parasite is the seal, with humans being an accidental host. Within the final host, it will undergo 2 additional molt cycles reaching adulthood in 15 to 25 days.¹⁷ The typical adult worm is approximately 61 to 82 mm for females and 54 to 64 mm for males. Human symptoms can present as early as 36 hours to 14 days after ingestion of the infected fish. The patient may present with nausea, emesis, severe abdominal pain, severe allergic reactions, and pain of the

pharynx and esophagus. The parasitic burden can result in anemia, formation of gastric ulcers, and rarely an anaphylactic reaction.⁵

Anisakis simplex “herring worm” belongs to a broad category of 2 different families, Anisakidae or Raphidascarididae. Currently, 3 species make up the *simplex* complex, which are *A. simplex* (*sensu stricto*) found in the northern Atlantic, *A. simplex C* found in the northern and southern Pacific waters, and *Anisakis pegreffii* found in the Mediterranean Sea.⁵ The differences in the 3 species are related to the geographic distribution of the host and the preference of a parasite for its host. The life cycle of Anisakidae begins with ingestion of the larva form by crustaceans such as crayfish, lobsters, and crabs, where the larva continues to develop. After consumption of the crustacean by its second host, marine fish, the parasite migrates into the intestinal mucosa and muscular tissues where it continues to mature. Upon ingestion by its final host, whales, dolphins, and porpoises—with humans being the accidental host—the parasite develops into its adult form.⁵ Several studies have shown at the death of its intermediate host that the larva will migrate from the viscera to the muscle layers, thereby making infection more likely with the ingestion of undercooked fish or squid.⁵ Infected humans may present for emergency care as early as 1 hour after ingestion of undercooked or raw fish. The parasite migrates deep into the mucosa of both the intestines and stomach, resulting in severe abdominal pain, nausea, and vomiting. Patients become very sick with presenting symptoms most closely mimicking peptic ulcer, appendicitis, or peritonitis. The most concerning presentation of the infection is a strong allergic reaction ranging from an urticarial rash to anaphylactic shock.

Fish Parasites and Pregnancy

Very little information is available about the specific effects of fish parasites on the pregnant patient and her unborn child. Therefore, we must extrapolate from the current literature about the overall effects of parasites on pregnancy and fetal development.

The initial response of the pregnant patient to the invading parasite is activation of the immune response. The immune system is a complex network involving a multitude of biological processes and events that lead to the body’s ability to mount a response in order to protect itself against a biological threat. In the clinical picture of helminth infection in pregnancy, the initial immune response is predominately an activation of eosinophils, basophils, and mast cells with release of multiple cytokines. The acute response can lead to a strong and severe immunopathologic reaction such as anaphylaxis that can lead

to harm and death to both mother and fetus. This type of reaction can be seen specifically with the fish parasite, *A. simplex*. Chronic long-term effects of infection can lead to anemia, malnutrition, suppression of immune responses allowing other opportunistic infections to cause disease, fetal growth restriction, fetal and placental infection, preterm birth, and “tolerance” (the down-regulation of the immune system) in newborns.^{11,14,24}

The normal immunologic response of a pregnant woman is far less effective because of the suppression of cell-mediated immunity, whereas normal humoral immunity is maintained. These changes occur at the maternal-fetal interface but also globally affect the immune response system, thereby increasing the susceptibility to certain intracellular pathogens such as parasites. Furthermore, the effectiveness and safety of treatment need to be weighed upon the overall benefit to the mother and fetus.

Ongoing anemia is a major health concern for women who are infected with parasites. A recent cluster randomized controlled study completed by Urassa et al⁷ in 2011 evaluated 3080 pregnant women with known intestinal parasitic infections and severe to moderate anemia as a result of parasitic infection. The pregnant women were treated with albendazole antepartum as well as postpartum. The investigators observed a dramatic decrease in the percentage of women with moderate and severe anemia. Of the 1475 women who were in the treatment arm, 73.8% had moderate anemia, and 5.8% had severe anemia. After those women received treatment at delivery, the rates dropped to 47% and 1.7%, respectively. These women were then followed up until their fourth month postpartum, with the rates of anemia dropping even further to 17.1% having moderate anemia and 1.0% with severe anemia. The overall pregnancy outcome was a moderate improvement in fetal birth weight and survival as well as a marked improvement in maternal anemia and overall health.^{7,19}

Treatment

The most effective form of treatment is prevention of the initial parasitic infection. Prevention of parasitic infection in pregnant women is of vital importance in overall health and nutritional status where both fetus and mother will benefit. Pregnant women should avoid raw and undercooked fish such as sushi, smoked or lightly seared seafood, and ceviche. All fish and fish byproducts should be thoroughly cooked at 56°C to 60°C for a minimum of 5 minutes prior to consumption. Alternatively, the parasites can also be eliminated by blast freezing the fish at –35°C for 15 hours or by regular freezing at –20°C for at least 24 hours and better if

up to 7 days prior to preparing.^{4,5} The fish can also be placed in a 12% brine solution of NaCl; however, this method can take from a few days up to weeks to be effective. It has also been observed that the larval stage of the *Diphyllbothrium* can survive for 4 to 8 hours at -8°C .³ Smoking fish does not appear to be effective in eliminating any stages of the fish parasite prior to consumption.³

Medical treatment for *D. latum* consists of a single oral dose of praziquantel, appropriately dosed. If the pregnant woman is unable to take praziquantel, the alternative is oral niclosamide. Both medications are category B drug, and dosages are listed in Table 2. Adverse effects most commonly associated with these medications are dizziness, headache, malaise, urticarial, abdominal distress, nausea, and fever. There is an approximately 1% risk that treated individuals may experience severe reactions such as cardiac arrhythmia and/or a Jarisch-Herxheimer reaction.

For women infected with *Pseudoterranova* and *Anisakis* species, the recommended medication is albendazole, which is continued for up to 21 days (Table 2). Although this medication is a category C, it is the most effective drug against both *Pseudoterranova* and *Anisakis*. The risks and benefits of this treatment must be reviewed, and clinical judgment should be used in determining the treatment that will be the most beneficial for the mother and her unborn child. Adverse effects of albendazole are similar to those associated with praziquantel; however, the severe adverse effects differ. The 2 associated severe adverse effects, although rare, are bone marrow suppression and acute liver failure. All women will need a negative test of cure following treatment.¹⁶

CONCLUSIONS

It is important for the overall health of a woman during pregnancy to avoid the ill effects from a parasitic worm infection. One of the more serious adverse effects worldwide is the development of maternal anemia, which affects more than 25% of pregnancies worldwide.¹³ An infected mother with a parasitic-induced microcytic anemia will have decreased circulating mature red blood cells, which may lead to a lack of appropriate oxygenation to the placental vascular bed and result in

limited oxygen and nutrients being supplied to the fetus. The end result of fetal anemia may be long-term impaired neurologic function and neonatal development.¹⁹ In addition with maternal hemorrhage being the leading cause of maternal mortality worldwide, the pregnant patient who is already anemic because of a parasitic infection has a higher likelihood of having significant morbidity or even mortality with delivery.

Microcytic anemia is not the only type of anemia affecting these women. A study completed by Scholz et al³ showed the parasite is able to interrupt the association between vitamin B₁₂ and intrinsic factor, leading to megaloblastic anemia by attaching at its preferred site, the terminal ileum, which is also the site of absorption and complex formation of vitamin B₁₂ and intrinsic factor. It has been observed that the higher the burden of infection, the more severe the deficiency of vitamin B₁₂, and the more severe the anemia. In severe cases, approximately 80% of vitamin B₁₂ can be absorbed by the parasite, leading to a 40% drop in overall vitamin B₁₂ stores.³ Maternal vitamin B₁₂ deficiency can lead to peripheral neuropathy and central nervous system degenerative lesions. In the fetus, this deficiency can lead to neural tube defects due to the lack of methionine synthase, which is a critical element needed for the development of the nervous system. In addition, a link has been established between the risk of intrauterine growth restriction (IUGR) and B₁₂ deficiency. In a cohort study conducted in India, there was a greater than 28.6% prevalence of IUGR in women lacking appropriate vitamin B₁₂ supplementation.²⁰

It has also been observed that the segments of the fish parasites can migrate into the biliary tract, which can result in cholecystitis and cholangitis.³ During a normal pregnancy, there is an overall 10% to 15% increase in biliary sludge. This increase also provides increased opportunity for the parasite to gain access to and settle within the biliary tract. Either of these events occurring in pregnancy may increase the morbidity and mortality of both mother and fetus. The addition of the lack of iron and/or vitamin B₁₂ in pregnancy due to helminth infection limits the ability of the fetus to grow and develop normally.

An ongoing study by Cooper¹¹ in women with known parasitic infections during pregnancy and continued infestation of the infant through early childhood

TABLE 2
Treatment Table

Parasite	Drug	Amount	Timeframe	Alternative Treatment
<i>D. latum</i>	Praziquantel	5–10 mg/kg	Single dose	Niclosamide at 50 mg/kg (max of 2 g) for 3 d
<i>P. decipiens</i>	Albendazole	400 mg twice daily	7–21 d	
<i>A. simplex</i>	Albendazole	400 mg twice daily	7–21 d	

revealed the down-regulation of the immune system limiting the child's ability to respond appropriately to vaccines resulting in both limited short- and long-term immunity. In addition, the cellular immunity defenses are further affected by a decrease in polymorphonuclear neutrophil function with decreased myeloperoxidase activity, impairment of intracellular bactericidal activity, thymic atrophy leading to decreased production of T lymphocytes, impaired natural killer cell activity, and impaired interleukin 2 production.⁸ The reduction in these factors can lead to a higher maternal susceptibility to infections and/or coinfections that further stress a pregnancy.

The major impact of a fish-borne parasitic infection is anemia and altered immunity that could lead to an increased risk of maternal infection. Other maternal effects could include small bowel obstruction, cholecystitis, and acute anaphylactic reaction. Fetal effects are the result of maternal infection and may include intrauterine growth restriction and preterm delivery.

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