NTDs are among the most common congenital abnormalities contributing to neonatal mortality and morbidity, secondary only to congenital heart defects (25). They occur when the neural tube fails to close completely within 28 days post-conception, often before a woman realizes she is pregnant (26). It is scientifically evident that folate supplementation in the periconceptional period can reduce the risk of NTDs by up to 70% (27-28).

Anencephaly and spina bifida are the most common NTD types. Annually, an estimated more than 300,000 newborns are affected by NTDs worldwide, although the prevalence of NTDs varies greatly between countries (26, 29). Anencephaly is characterized by an open neural tube in the cephalic region with total or partial absence of the brain and skull (26). Spina bifida is characterized by herniation of the meninges and or neural tissue through a bony defect in the posterior vertebral arches (25). The prognosis of NTDs varies considerably according to the defect type: anencephaly is incompatible with survival and all affected infants are stillborn or die soon after delivery. However, many infants born with spina bifida survive, suffering from disabilities such as paraplegy, loss of bladder and bowel control, hydrocephalus and learning disabilities, hence compromised health-related quality of life (30-37).

The etiology of NTDs is not fully understood but thought to be multifactorial; however, the development of an NTD is considered to be influenced by both genetic and environmental factors. Evidence for a genetic contribution to the development of NTDs is based on an association between NTDs and chromosomal and single-gene disorders, and an increased recurrence of NTDs in siblings (38-40). Many environmental factors are thought to predispose to NTDs. The factor that is considered to play a major role is maternal folate status in the periconceptional period (41). The risk of an NTD-affected pregnancy reduces as RBC folate levels increase. It has been calculated that periconceptional maternal RBC folate concentrations of 906 nmol/l (tg/ml) or higher are associated with a very low risk of NTDs (0.8 per 1,000 births) (41).

III- Why is the Reduction in the Incidence of NTDs Below Expectation?

- There are currently three possible ways to increase women’s folate intake:
  1. Increasing consumption of food rich in naturally occurring folate
  2. Consuming food fortified with folic acid
  3. Taking folate supplements as in pills.

- However, even with the implementation of these strategies, decreases in NTD rates have fallen short of expectations (42-43), as outlined below:

A- Increased intake of foods naturally rich in folate is relatively ineffective:

- Naturalfolate is found in a variety of foods, including broccoli, leafy green vegetables and citrus fruits (1).
- Natural food folates have limited ability to boost folate levels due to their incomplete bioavailability and poor stability under cooking conditions (44).
- Many natural folates need to be metabolized before they become biologically active (1).
- A typical diet, as consumed in most western countries, does not generally provide enough folate to achieve the levels associated with the lowest risk of NTDs (45).
- Women with certain polymorphisms of folate-converting enzymes have difficulty metabolizing some natural folates (1, 46).
- Therefore, increasing consumption of foods naturally rich in folate is relatively ineffective means of boosting folate levels compared with folic acid supplementation or consumption of fortified foods (45, 47, 48).

B- Effect of fortification of foods with synthetic folic acid is below expectations:

- In most European governments and/or national societies recommend periconceptional folic acid intake of 400 μg daily for at least one month prior to conception and for the first three months of pregnancy (19-20).
- In the USA, current recommendations specify that all women of childbearing potential consumed the recommended folate intake (24).
- In 1998, the Food and Drug Administration (FDA) mandated that all cereal grain products be fortified with folic acid 140 μg/100 g in order to increase folic acid intake in the general population by 100 μg/day (55-56). However, following increases in serum folate levels, a decline in both plasma and RBC folate levels has been observed since 2000 in the USA (57-58).

C- Periconceptional dietary folate supplementation is often underused:

- There is a large body of evidence confirming that folate supplementation in the periconceptional period significantly reduces the risk of NTDs (6-18).
- A Cochrane review of five randomized trials showed a protective effect of daily folic acid supplementation in preventing NTDs (risk ratio 0.28 with a 95% confidence interval 0.15-0.52) compared with placebo or vitamins and minerals without folic acid (27).
- Many health authorities worldwide recommend folate supplementation, for example:
  - Most European governments and/or national societies recommend periconceptional folic acid intake of 400 μg daily for at least one month prior to conception and for the first three months of pregnancy (19-20).
  - In the USA, current recommendations specify that all women of childbearing potential consumed the recommended folate intake (24).
- Folate intake is needed well in advance of conception to reach adequate folate levels at the time of neurolation. There is large data to suggest that the recommended period of preconceptional folic acid supplementation should be increased from four to 12 weeks in order to achieve maximum NTD risk reduction (59).
As outlined previously, many women find it difficult to remember to take a vitamin pill on a regular basis (60). In contrast, compliance with COCs can generally be regarded as high, as the consequences of one missed pill may be more likely to be significant. Many women, however, do not have optimal folate levels at the time of conception, and many of those who do not have adequate folate levels at the time of conception may increase the likelihood of them having increased folate levels at the time of conception.

- As for all COCs, women should be encouraged to continue their current pill-taking behavior.
- In pill-taking behavior.

Many women do not seek advice from their physician regarding the importance of folate supplementation (61,63).

Many worldwide health organizations recommend supplementing with 400 μg/day folic acid in the periconceptional period (21,51).

COCs would be a reasonable delivery vehicle for folate supplementation in women of childbearing age for many reasons:

- Targeted approach to folate supplementation

COC users are women of childbearing age, i.e., those members of the population in whom adequate levels of folate are of the greatest benefit.

- Timely intake of folate supplementation

Combining a COC with folic acid ensures that women of childbearing age receive the widely recommended daily dose of folate in the periconceptional period.

- Women who receive folic acid with their COC on a daily basis, and then continue to take a folic acid supplement as soon as they discontinue their pill, are more likely to have adequate folate levels at the time of conception.

- Regular intake of folic acid supplementation

Combining a COC, which has a generally high level of user compliance, with the recommended daily dose of folic acid in a single pill offers the potential for improved folate status in COC users without requiring any change in pill-taking behavior.

V- Summary of Combination: COC + Folate

- Folate is an essential vitamin that is critical for DNA synthesis and normal cell division (1,2).
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- The risk of NTD-affected pregnancies can be reduced through adequate folic acid intake at the right time (27).

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B- Timely intake of folate supplementation

- As outlined previously, NTDs occur within the first 28 days of conception, within 14 days after the first day of missed periods (26).
- Many women, however, do not have optimal folate levels at the time of conception, due to various factors including:
  - Lack of awareness.
  - In a 2010 survey of nearly 23,000 women in 18 European countries, of the women with children who were currently aware of the benefits of folic acid, only 35% knew about folic acid’s benefits related to birth defects while thinking of becoming pregnant and/or
  - Many women do not seek advice from their physician regarding the importance of folate supplementation (61,63).

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