

**Exploring the Complex Relationship Between Psychological Stress and  
Fertility: Implications for Population Growth in Developing Countries.**

UNDER PEER REVIEW

## Abstract

Uncontrolled population growth has raised serious concerns among future policymakers. Although fertility rate has declined substantially over time, in developing countries the rate is still very high. Most of these countries face serious issues such as; severe poverty, malnutrition, unemployment, homelessness, financial insecurity, and medical insufficiency, leading to **psychological distress**. This article explores the mechanisms of psychological stress and its potential effects on human fertility. An attempt is made to differ from the existing claim that stress is anti-steroidogenic. **This counter was based on earlier studies on adaptation of acute stress and overcoming stress stimuli.** Which have asserted that individual adaptive abilities can alter the negative outcome of psychological stress depending on genetic, environmental, and behavioural factors. **One of such adaptations comes from mitochondrial efficiency.** An extensive energy demand during stress is achieved through **competitive mitochondrial biogenesis.** Earlier studies have noted that psychological stress triggers mitochondrial biogenesis. **Thus, theoretically, mitochondrial biogenesis may also contribute in augmenting quality of sperm.** In conclusion, stress induced biogenesis of mitochondria may contribute in enhancing fertility. Future studies on the degree of psychological stress and its possible retaliation through **mitochondrial biogenesis, and subsequent responses to metabolic, and mechanical pathways,** would open new avenues in understanding human fertility.

Keywords: Psychological stress, Fertility rate, Mitochondrial biogenesis, Anxiety and depression

## **Introduction**

Depending on its perception and controllability, stress has both objective and subjective components.<sup>1</sup> It is likely that individuals may react differently to the same stressor. When anticipating a stressor, the resulting responses depend on how promptly and effectively an adaptation mechanism is established. Previous reports suggest that most chronic stresses are damaging to health and well-being<sup>2</sup>, whereas, acute stresses are more common and generally stimulate thrill and excitement. Most of the short periodic stresses are adaptive but do not prevent the damages caused by sudden alterations in hormonal homeostasis.

Although stress is generally considered harmful to human health and well-being, it has also assisted in aiding the evolutionary process of adaptations. Adaptation is key to higher population growth. The current rates of population growth across various countries demonstrate significant variation in relation to their respective socio-economic conditions. A clear correlation exists between elevated population growth rates and lower socio-economic status, suggesting that demographic trends are intricately linked to broader economic and social inequalities. In this article, several facts from previous studies are reviewed to support our hypothesis that, despite persistent psychological stress, the surprisingly high fertility rate in developing countries contradict the current notion of its negative impact on reproductive health and fertility.

### **Population growth- world perspective**

The global population growth rate has never declined except for two major incidents; one, the World War II and second, the killings of 30 million people in China during 1958-1961 (Great Leap Forward). Today we count more than 7.71 billion with an estimated growth rate of 1.07% per year ([www.worldometers.info/world-population](http://www.worldometers.info/world-population)). Though population growth rate has declined in the last three decades, it is assumable that the global population

will continue to grow in the 21st century. Country-wise data for population growth suggests that developing countries have a much higher growth rate than developed countries.<sup>3</sup> A study by Gu et al. (2021)<sup>4</sup> reported that in high income countries the total fertility rate have been below replacement level, amounting less than 1.5 births per women for past several years. The total fertility rate in developing countries, estimated to be between 3-5% from 1995 to 2000<sup>5</sup>, has certainly declined compared to earlier rates but remains higher than that of most developed countries.

### **Why developing countries have a huge population growth rate**

One of the reasons for developing countries to have a higher population growth is the absence of an effective, safe, feasible and low-cost contraceptive method.<sup>6</sup> Additionally, the lack of family planning, awareness, sex education and ineffective government-led policies also contribute to uncontrolled population growth. Lack of equality in gender contribution towards family planning is also one of the reasons for increased population growth in developing countries. Most of these countries have patriarchal societies, thus the usability of male contraceptives is highly unlikely.<sup>7</sup> However, it cannot be denied that the mortality rate across all age groups is also equally high in developing countries.<sup>8</sup> There is also possibility of other factors that enhance the fertility rate altogether such as early marriage, religious encouragement, parental encouragement, social influence, more time at home due to unemployment, non-working female partners, etc. In general, all the above factors are important in enhancing fertility rate in developing countries; nevertheless, the combined effects of these factors are most likely to lead to stress and depression. A study by Hall et al.,<sup>9</sup> reported that women with higher stress and depression were more sexually active than those who were less stressed and depressed. Sexual intercourse among stressed people is also common due to its counterproductive effect of relief from tense situations.<sup>10</sup>

### **Prevalence of stress in developing countries**

It is surprising that nearly 16% of the global population is affected by major depressive disorders.<sup>11</sup> Depression is one of the major causes of morbidity and disability in developing countries.<sup>12</sup> A cross-sectional study reveals that nearly 35% of the sampled population of factory workers in developing countries experience anxiety, sleep disturbance, depression, somatic complaints and various other types of stresses.<sup>13</sup> A study by Patel and Klienman,<sup>14</sup> reviewed the poverty risk relationship in developing countries. Their study explains poverty and socioeconomic status as a few of the most influencing factors that cause emotional distress. Various factors such as income, insecurity, hopelessness, social change, education, gender, and co-morbidity were used to establish the relationship between poverty and common mental disorders.<sup>14</sup>

#### **Are stress and depression related to each other?**

Reports are stating that stressful conditions such as losing jobs and loved ones, financial crisis, and insecurity cause the onset of depression.<sup>15,16</sup> Where depression is a key health issue affecting the quality of life, medical morbidity and mortality globally,<sup>17,18</sup> stress, on the other hand, is not always harmful. It is a key for survival; human evolution may not have occurred, had it not overcome subsequent stresses during critical adaptations. Worthman<sup>19</sup> explains 'stress' as evolutionary adaptations against threats and damages to well-being. Studies show that stress has various positive effects, depending on personalities. For example, being in traffic can have differential effects on individuals, based on personality, social support, health and socioeconomic status. It is also dependent on individual conditions such as mood, self-efficacy and physical symptoms.<sup>20-23</sup> A study suggests that daily stressful events enhance one's response to difficult events, it also buffers one from future harmful effects of similar stressor.<sup>24</sup>

#### **Mechanism of psychological stress**

Stress is a complex process which causes emotional breakdown under psychological pressure or unexpected problems. It is a condition of uncomfortable emotional experiences causing biochemical, physiological and behavioural alterations.<sup>25</sup> Various factors influence stress. Table 1 lists out the major factors that play important roles in physical and psychological expression of stress.

There are three physiological systems that are directly involved in psychological stress; 1) the nervous system, 2) the endocrine system and 3) the immune system.<sup>40</sup> Endocrine system regulates gland and organs that synthesize and release hormones that control growth, development, metabolism and reproduction. Previous studies suggested that two endocrine responses are mostly responsible for negative effects of stress 1) Hypothalamic Pituitary Adrenocortical axis (HPA) and Sympathetic Adrenal Medullary (SAM). The HPA is a set of direct influences that communicate between hypothalamus, pituitary and adrenal glands. Whereas, SAM is a neuroendocrine stress-response system, that regulates hormones such as epinephrine and norepinephrine.

The effect of diurnal cortisol is one of the key markers of psychological stress. Cortisol is a hormone produced in adrenal cortex within the adrenal gland.<sup>41</sup> Humans have unique diurnal cycles of cortisol levels, which are high in the mornings and low at mid-night.<sup>42</sup> It is responsible for the activation of the HPA axis, which triggers inflammatory responses, and regulates the metabolism of carbohydrates, lipids, proteins and gluconeogenesis. Earlier studies report that sustained stress can cause high level of circulating cortisol, leading to allostatic load.<sup>43</sup> However, it is unclear how chronic stress alter the hypothalamic-pituitary-adrenal axis or *vice versa*.

On the other side SAM activation plays an important role in the modulation of cardiovascular, pulmonary, hepatic, skeletal muscle and immune systems. Secretion of catecholamine occurs in response to SAM activation.<sup>[44]</sup> Earlier studies reported that repeated

exposure to stressful stimulus for several weeks cause numerous adaptive alterations in SAM.<sup>45</sup> The pattern of adaptation shown in the study carried out by McCarty et al.,<sup>45</sup> indicated resemblance to processes of habituation and sensitization. Prolonged activation of HPA and SAM can interfere with various physiological systems causing risk of psychological disorders.<sup>46,47</sup>

Apart from cortisol and catecholamine, vasopressin,<sup>48</sup> gonadotropin,<sup>49,50</sup> and insulin<sup>51</sup> are also regulated by psychological stress. Indirect regulation of other hormones is also linked to stress, such as growth hormone through its insulin-antagonistic effect,<sup>52,53</sup> prolactin via vasopressin and peptide histidine levels<sup>54</sup> and thyroid hormone through the effect of glucocorticoids on the central nervous system, which in turn regulates gonadotropin.<sup>55,56</sup> The diagram below shows the possible alterations in hormonal status during psychological stress (Figure 1).

### **How does stress influence fertility?**

There are various studies available which report negative impact of psychological stress on reproductive health of both female<sup>57-59</sup> and male<sup>60-62</sup>. In females, infertility causes elevated anxiety and depression due to shame, guilt, social taunts and reduced self-esteem.<sup>63,64</sup> However, it is not clear if anxiety and depression cause infertility in females. In an interesting review by Rooney et al.,<sup>65</sup> the author claims that psychological interventions to decrease anxiety and depression lead to a significant increase in pregnancy rate.

In male, psychological stress reportedly plays an important role in reducing paternity and abnormal semen profile. The review article by Nargund<sup>66</sup> claims that HPA axis has a direct inhibitory action on the hypothalamic-pituitary-gonadal (HPG) axis and Leydig cells in the testis. There is ample information available that products of HPG axis modulate functions

of the HPA axis.<sup>67-69</sup> There are also claims that mild to severe emotional stress decrease testosterone level and possibly participate in reducing spermatogenesis.<sup>70</sup>

### **Can stress increase fertility?**

Arguably, even if both male and female respond negatively to psychological stress, it is difficult to deny the remarkable surge in population growth in developing countries with higher level of psychological stress. It is a valid question whether mental stress somehow acts in reverse. Or can we just for instance, assume that our interpretation of psychological stress on reproductive health is not categorised based on the degree of successful adaptations. For example, most of the studies on psychological stress claiming adverse effect on reproductive system are based on excessive imposition of induced stress, such as; Arun et al.;<sup>71</sup> Gomes et al.;<sup>72</sup> Padoin et al.;<sup>73</sup> McGrady and Chakraborty<sup>74</sup> etc. These studies possibly do not replicate the actuality of human psychological stress entirely, as stress is a complex process and one of the keys to survival. Stressors have deleterious effects on the cellular processes, nonetheless, simultaneously it encourages various adaptive responses to reduce damages and maintain normalcy in the cell. Mitochondria is considered a key organelle that responds to stresses, such as; 'fight and flight response' by maintaining a huge amount of energy demand.<sup>75,76</sup> In contrast to a study carried out by McGrady,<sup>70</sup> a study by Gak et al.,<sup>77</sup> reports that psychological stress triggers mitochondrial biogenesis which encourages adaptive mechanism in testosterone producing Leydig cells.

The study by Gak et al.,<sup>77</sup> also reports that acute stress activates PGC1 protein that is required for the production of new mitochondria and assist against oxidative stress related damages. Previous studies claim that the activity of mitochondria (mitochondrial protein import machinery and mitochondrial fusion) is important for steroid genesis in Leydig cells.<sup>78-83</sup> Interestingly, mitochondria also play an important role in male fertilization. Mitochondria of the spermatozoa are tightly wrapped around the axoneme, at the mid-piece.<sup>84</sup>

These power plants are vital for sperm motility and to ensure male fertility. Hyperactivated motility at the site of fertilization is dependent on mitochondria for an adequate supply of energy that is utilized by the flagellar dynein-ATPase.<sup>85,86</sup> A detailed review by Piomboni et al.,<sup>87</sup> on the role of mitochondria in sperm motility, concluded by suggesting that deeper study on mitochondrial functions will open new possibilities to understand bioenergetics of sperm mitochondria and fertility. It is interesting to note that a typical mammalian sperm mid-piece contains 50-75 mitochondria, whereas, the mammalian oocyte contains around  $10^5$ - $10^8$  mitochondria.<sup>88</sup> The numbers of mitochondria in both sperms and oocytes indicate a high demand of energy for successful fertilization. Thus, the production of new mitochondria can invariably support fertilization.

## Conclusion

Stress can be both adaptive and threatening depending on various factors such as; genetic, behavioural and environmental. These factors individually or in combination provide adaptive coping resources to individuals. Any positive adaptive ability is a process of refinement in the course of evolution. This article concludes that adaptable psychological stress can affect fertility, completely opposite to anxiety and depression. Therefore, it is possible that human reproducibility may increase in a stressful environment through mitochondrial biogenesis. Nevertheless, there is more to be explored, for better understanding of role of stress in human fertility. Further study on mitochondrial biogenesis, steroidogenesis and subsequent alterations in metabolic and mechanical pathways of germ cell development would provide valuable insight in the area.

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Table 1: List of psychological stress associated factors

Factors		References
Environmental factors		
Chronic stressors	Allostatic load	26
Stressor diversity	High diversity lead to high negative impact	27
Physiological factors		
Telomeres	Shortening of telomeres is associated with stress	28-30
Circulating inflammatory markers	Interleukin 6 and C-reactive protein	31
Electrodermal activity	Hypo-activation of diurnal cortisol	32
Attention and memory		
Prefrontal cortex	Negative impact (Psychological stress triggers release of noradrenaline and dopamine)	33-35
Hippocampus	Negative impact (Reduced volume) (triggers release of glucocorticoids)	36-38
Decision making	Diurnal cortisol rhythm	39

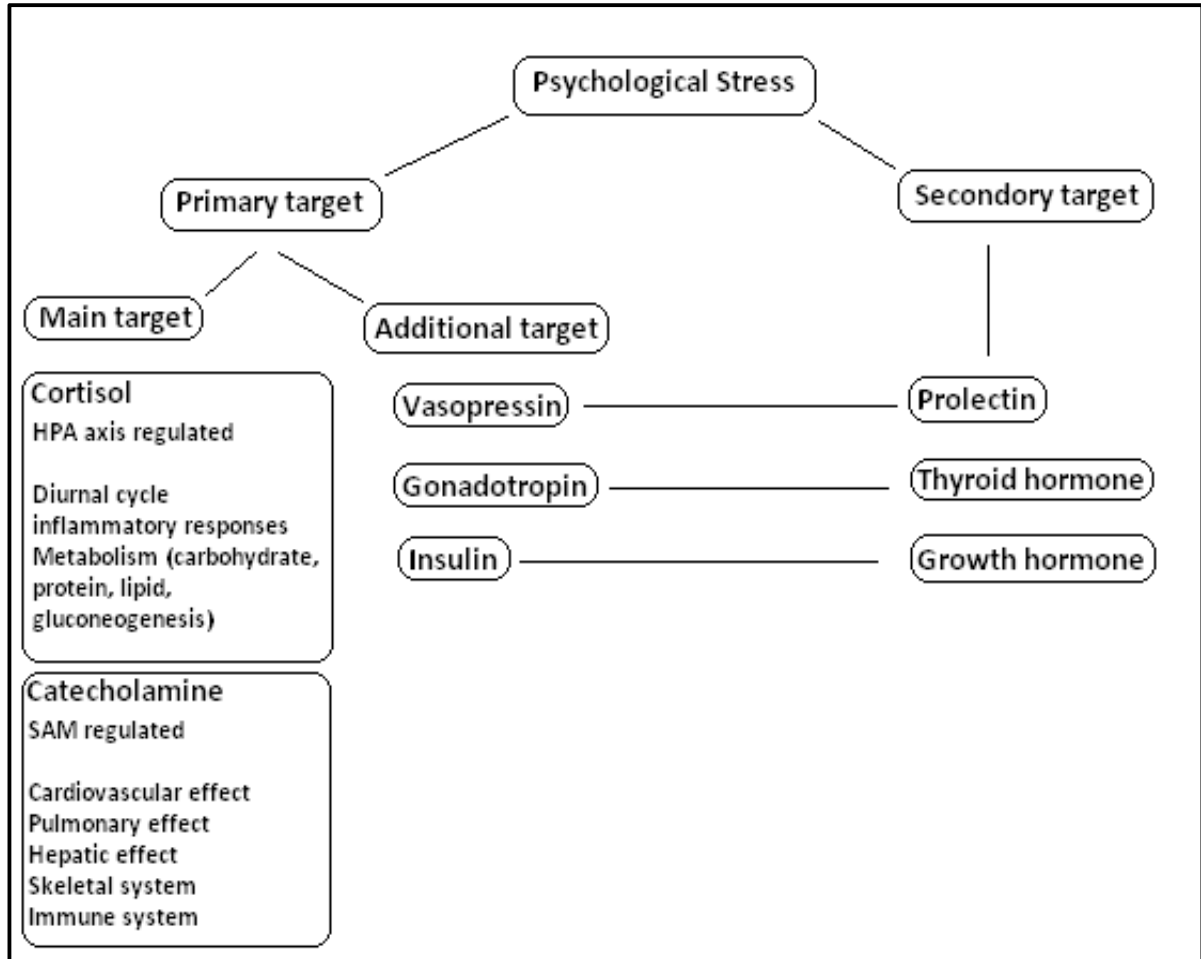


Figure 1: Diagram shows possible targets of psychological stress and its consequential metabolic effect.